REMARKS

In order to simplify the issues under consideration in this case, claim 60 and all claims dependent thereon, have been canceled. In addition, claim 24 and all claims dependent thereon have been amended to delete the recitation of antibody fragments. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. Applicant respectfully requests further consideration of the present application in light of the following remarks.

Independent claim 24 is directed to a treatment method that uses an immunoconjugate that comprises (i) at least one human, humanized or chimeric anti-CD22 antibody, and (ii) a drug or a radioisotope, wherein said radioisotope is other than ^{131}I, wherein the immunoconjugate is used in combination with a naked anti-CD2O mAb. None of the cited references disclose or teach the combination of anti-CD22 immunoconjugate and naked anti-CD20 antibody as described in claim 24 and claims dependent thereon.

Claims 60-70, 73-79 and 91-93 are rejected under 35 U.S.C. §102(e) based on United States Patent No. 5,789,554 and claims 60-70, 73-77, 79 and 91-93 are rejected under 35 U.S.C. §102 (b) based on WO 96/04925. Claims 60-65, 67-69 and 91-95 are rejected under 35 U.S.C. §102(b) based on Juweid *et al.*, and claims 60-89 and 91-97 are rejected under 35 U.S.C. §103(a) based on Juweid *et al.* in view of United States Patent No. 5,698,178. All of these rejections are obviated by the cancellation of claims 60-97.

Claims 24-26, 36-38, 44, 45, 47, 52, 55-57, 60-70, 73-79 and 91-93 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and Li *et al.* Claims 24-27, 36-38, 44, 45, 52, 55-57, 60-70, 73-79 and 91-93 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,106,955. Claims 24-26, 36-42, 44, 45, 52, 55-57, 60-70, 73-77 and 91-93 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,686,072 and PCT publication WO 95/09917. Claims 24-26, 36-39, 44, 45, 52, 55-57, 60-70, 73-77 and 91-93 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and European Patent Application No. 510949. Claims 24-27, 36-38, 43-45, 52, and 55-89 and

91-97 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,698,178. Claims 24-27, 38, 43-45, 52, 55-89 and 91-97 are rejected under 35 U.S.C. §103(a) based on WO 96/04925 in view of Maloney *et al.* and United States Patent No. 5,698,178.

All of these rejections are based on the combination of United States Patent No. 5,789,554 ("Leung") in view of Maloney *et al.* ("Maloney") with the addition of one or two additional references, and Maloney is the sole reference cited in support of the obviousness of combinations of anti-CD22 immunoconjugates and anti-CD20 naked antibodies. Therefore, once the impropriety of this portion of the rejection is established, all of the rejections based on Leung and Maloney must fall.

Leung describes immunoconjugates of LL2 with cytotoxic agents or labels (see abstract). The examiner admits that Leung does not teach combinations of LL2 with anti-CD20 antibodies as recited in claim 24 and claims dependent thereon, but urges that it would have been obvious to combine anti-CD22 immunoconjugates and naked anti-CD20 antibodies based on the disclosure in Maloney of treating B-cell lymphoma, NHL, and other leukemias and lymphomas with a chimeric anti-CD20 monoclonal antibody, rituximab. She argues that a skilled artisan would have expected a mixture of antibodies to the different epitopes "would be more efficacious in therapeutic methods, as well as enhance the treatment modality," citing the last paragraph on page 2465 of Maloney.

The cited portion of Maloney discloses that "extension of these studies to patients with minimal disease, using antibody alone or in combination with ***conventional therapies***, may provide the greatest benefit. "Conventional therapies" at the time of the Maloney article, circa 1994, were chemotherapies, not antibody therapies. Therefore, the disclosure in Maloney that anti-CD20 may be combined with a "conventional therapy" would not have suggested a combination with anti-CD22 immunoconjugate therapy, as presently claimed. No *prima facie* case of obviousness exists.

Moreover, Maloney *teaches away* from any use of immunoconjugates, and thus is improperly combined with Leung to allege the obviousness of the presently recited combination. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, ***would be discouraged*** from following the path set out in the reference, or would be

led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 31 U.S.P.Q.2d 1130 (Fed. Cir. 1994), emphasis added. More recently, in *Ecolochem, Inc. v. Southern California Edison Company*, 227 F.3d 1361 (Fed.Cir. 2000), cert. den., 121 S.Ct. 1607, the Federal Circuit noted that the combination of two prior art references does not render patent claims obvious if there was no evidence of any suggestion, teaching, or motivation to combine the information from the prior art and where there was evidence that the prior art actually taught away from the patented process. In *Ecolochem*, the prior art taught away from a mixed-bed ion exchange process; therefore, no motivation existed for one of ordinary skill in the art to produce the patented technology.

Similarly, here Maloney teaches away from the use of antibodies that are radiolabeled or conjugated to a cytotoxic agent, noting that:

> The [anti-CD20] antibody preparation is used directly for therapy, not requiring conjugation to drugs, toxins, or radiolabels, each of which requires extensive safety testing and may not be stable after formation of the active conjugate. Antibody modification may interfere with antigen binding... significant hematologic toxicity is associated with the use of high-dose radiolabeled conjugates...In some studies, immunotoxin conjugates have been associated with significant toxicities (page 2585, penultimate paragraph).

Thus, a skilled artisan ***would be discouraged*** from the very combination urged to have been obvious by the examiner. The combination of Leung and Maloney would not have suggested therapy with a combination of an anti-CD22 immunoconjugate and a naked anti-CD20 antibody. No *prima facie* case of obviousness of claim 24 and claims dependent thereon is supportable based upon the combination of a primary reference that teaches the use of immunoconjugates (Leung) and a secondary reference (Maloney) that teaches the use of naked antibodies and specifically teaches away from any use of immunoconjugates.

In an Advisory Action dated June 23, 2006, the examiner commented that "anti-CD20 is regarded as a conventional therapy because conventional means developed or established practice. This meaning does not preclude the CD20 antibody taught by Maloney in 1994." Even assuming, for the moment, that the allegation that anti-CD20 antibody therapy was "conventional" in 1994, the examiner has failed to state a *prima facie* case of obviousness. That is, if the examiner truly meant to say that the meaning of conventional therapies did not preclude

anti-CD20 antibody, then the result would be to add CD20 antibody as a "conventional therapy" to the CD20 antibody taught by Maloney as a single agent therapeutic. This is not a combination therapy as taught by applicants, in which a naked anti-CD20 mAb is combined with at least one human, humanized or chimeric ***anti-CD22*** antibody labeled with a drug or a radioisotope other than ^{131}I. No *prima facie* case has even been set forth.

Maloney suggests the possible implementation of further studies in which the CD20 antibody is combined with "conventional therapies." If the examiner meant to urge that all antibody therapy was "conventional" as of 1994, such that a skilled artisan would have been motivated to combine a different antibody, such as an anti-CD22 antibody, in treatment based on Maloney's comment regarding the addition of "conventional therapies" to his anti-CD20 antibody, this is unsupported by anything in the record. Certainly Maloney itself does not support the examiner's statement that treatment with anti-CD20 antibody was "conventional therapy" in 1994. Maloney is a report of results from a ***Phase I clinical trial*** to evaluate the safety of anti-CD20 antibody as a single agent therapeutic. A Phase I trial is the earliest stage in clinical trials of an ***investigational drug*** – and therefore Maloney is antithetical to the examiner's conclusion that treatment with anti-CD20 antibody constituted "conventional therapy." "Conventional" means "conforming to established practice or accepted standards; traditional" (The American Heritage® Dictionary of the English Language: Fourth Edition - 2000). An investigational drug in Phase I clinical trials cannot be considered a conventional therapy, *i.e.*, it does ***not*** conform to established practice or accepted standards." By definition, investigational drugs have not been "accepted." Companies can provide investigational drugs to doctors if they are part of a drug trial covered by an FDA-approved protocol, and such drugs are ***by definition <u>not</u> conventional***, since they are not available for use by any doctor on any patient.

The first approved antibody for therapy of any malignancy was the anti-CD20 antibody rituximab that is the subject of Maloney. It was not approved until 1997, and therefore there was no cancer therapy with any antibody that was a conventional therapy in 1994, let alone a combination therapy with multiple antibodies. Even today, after the advantage of epratuzumab combined with rituximab has been published, this combination has not been approved and hence is ***not*** conventional therapy. In fact, ***no antibody combination has ever been approved***.

Current reviews and texts support the fact that combination antibody therapy is not conventional. Some articles began to discuss the possibility of such combination therapies following applicant's publication of their studies of epratuzumab and rituximab in about 2002/2003, but none indicate that such therapy is "conventional." The following articles show that antibody therapy generally, and combination antibody therapy in particular is not considered "conventional" in the art, even today:

- Hiddemann in 1995 states that "more experimental approaches consist of the application of immunotoxins or radioisotopes, coupled to monoclonal antibodies directed against lymphoma-specific antigen" for the treatment of NHL, *i.e.*, even single antibody therapy was considered an "experimental approach and not a conventional therapy. *Eur. J. Cancer*, 31A(13-14):2141-5 (1995).

- Skarin *et al.* in 1997 alludes to "the use of specific monoclonal antibodies directed against cell surface antigens has contributed to the understanding of [NHL]." That is, the antibodies were considered useful in understanding NHL, but not in therapy. With respect to therapy, Skarin *et al.* list "combination chemotherapy without or without regional radiotherapy." *CA Cancer J. Clin.*, 47(6):351-72 (1997).

- An educational review published in 1998 notes under the heading "Monoclonal Antibodies" that:

  > New treatment approaches for low-grade lymphoma include monoclonal antibodies that attach to receptors found on B-lymphocytes. One general approach uses radiolabeled antibodies; another uses a "naked" antibody. *Preliminary studies of these monoclonal antibodies as single agents* has demonstrated encouraging response rates and some evidence of long-term disease control, but the median duration of response and impact on overall survival are still unknown.
  >
  > Webster *et al.*, *Oncology*, 12(5):697-714 (1998) -- emphasis added.

- In 1999, Czuczman *et al.* showed that a combination treatment of anti-CD20 monoclonal antibody and CHOP chemotherapy (a "conventional therapy") showed improved efficacy. This is a treatment of anti-CD20 antibody and

conventional therapy as mentioned in Maloney, but does not suggest combination antibody therapy. *Journal of Clinical Oncology*, 17:268, (1999).

- In an article about the current therapeutic paradigm for the treatment of NHL, Fisher in 2000 noted that patients with indolent NHL may be treated with single-agent alkylating agents, radiation therapy, or combination chemotherapy, while indicating that none of these approaches have produced curative results. Fisher notes the need for "innovative treatment strategies," and mentions the use of interferon, monoclonal antibodies with or without radioisotopes, purine analogues, and even high-dose therapy with stem-cell rescue are under investigation. Thus, in 2000, each of these was still considered investigational, and combinations of antibodies are not suggested. *Semin Oncol.* Dec; 27(6 Suppl 12):2-8 (2000).

- "What is New in Lymphoma," published in 2004, cites rituximab as an advancement in the treatment of NHL. Efforts to improve the activity of rituximab are noted, and include increasing the number of weekly infusions, delivering higher doses and increasing dose density. Combinations with CHOP are also mentioned. A Phase II study of a combination of rituximab with epratuzumab reported in 2003 and a phase I/II study of the combination of galizimab are mentioned, demonstrating that combination antibody therapy was still very much investigational at this later date. Cheson, *CA Cancer J Clin.* Sep-Oct; 54(5):260-72 (2004)

- The 2003 Merck Manual lists "many new treatments ... for indolent lymphomas. These include monoclonal antibodies, which bind to lymphoma cells and kill them. These antibodies (immunoglobulins), such as rituximab, are given intravenously. Sometimes, the monoclonal antibodies are modified so that they can carry radioactive particles or toxic chemicals directly to the cancer cells in different parts of the body. It remains uncertain whether these monoclonal antibodies can cure non-Hodgkin's lymphomas, or if they can achieve better results when combined with chemotherapy. Combinations with other antibodies are not included in the list of conventional or new therapies.

Indeed, even later articles published by IDEC fail to suggest combinations of their anti-CD20 antibody with other antibodies. In 2001, they published "Non-Hodgkin's lymphoma: review of conventional treatments" (*Curr Pharm Biotechnol.*, 2(4):279-91 (2001)), which states that:

> Conventional treatment for patients with newly-diagnosed non-Hodgkin's lymphoma (NHL) includes radiation or chemotherapy. In addition, those with asymptomatic low-grade disease may follow a "watch and wait" approach. Single agent oral alkylating therapy and CVP (cyclophosphamide, vincristine, and prednisone) have become a mainstay of treatment for low-grade NHL. High intensity chemotherapy consisting of the anthracycline, doxorubicin along with cyclophosphamide, vincristine and prednisone (CHOP) is offered as standard treatment for intermediate-grade NHL... Novel approaches to treatment are therefore needed. Monoclonal antibodies may fulfill this need, administered either as single agents or in conjunction with conventional cytotoxic approaches.

And in 2000, Maloney himself published "Monoclonal antibodies in lymphoid neoplasia: principles for optimal combined therapy," (*Semin Hematol*, 37(4 Suppl 7):17-26 (2000)), which speaks of the possibility of trying "novel combinations" and suggests that randomized, prospective trials are required to determine clinical utility. Thus, statements in later IDEC articles, including one by Maloney, contravene the examiner's position that Maloney's mention in 1994 of a combination of anti-CD20 antibody with "conventional therapies" would encompass combination antibody therapy as presently claimed.

Claims 24-27, 36-45, 47, 52, 55-89 and 91-97 are provisionally rejected under the doctrine of obviousness-type double patenting over claims 24-44 of co-pending application No. 10/3 14,330. The examiner states that applicant's request has been considered but found unpersuasive and the rejection is maintained. Applicant did not request that the rejection be withdrawn, but merely that it be held in abeyance until such time as allowable subject matter is indicated in one of the two applications. Until such time, the rejection is "provisional" and is indicated as such in the Official Action. According to MPEP 822.01:

> The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection

> remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

Thus, no further action on applicant's part with respect to the provisional double patenting rejection is required. Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

If there are any problems with this response, Applicant's attorney would appreciate a telephone call. In view of the foregoing, it is believed none of the references, taken singly or in combination, disclose the claimed invention. Accordingly, this application is believed to be in condition for allowance, the notice of which is respectfully requested.

Respectfully submitted,

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Non-Hodgkin's lymphomas--current status of therapy and future perspectives.

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Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of disorders which can either be classified according to their biology, represented by corresponding counterparts of normal lymphocyte development as in the Kiel classification, or according to their clinical course, used in the Working Formulation. The recently proposed Revised European-American Lymphoma (R.E.A.L.) classification may unify both aspects and facilitate the comparability of international studies. Besides histology, the extent of disease still comprises the major determinant of therapy. In high-grade lymphomas combination chemotherapy with cyclophosphamide, hydroxydaunorubin, vincristine and prednisone (CHOP) represents the treatment of first choice, and may be restricted to 3-4 cycles in patients with limited stages of the disease when followed by involved field radiotherapy. In more extended, bulky stage II to IV disease, treatment must be extended to six courses of CHOP and, potentially, additional irradiation. Even in advanced states of the disease, long-term remission and potential cure are achieved in 30-50% of cases. In low-grade lymphomas, most patients present with advanced stages III and IV for which chemotherapy can be applied with palliative intention only. Hence, a watch-and-wait approach still seems appropriate outside clinical investigations until the disease requires a therapeutic intervention. This consists preferentially of chemotherapy of moderate intensity such as cyclophosphamide, vincristine and prednisone (COP) or prednimustine and mitoxantrone (PmM). In responding patients, maintenance therapy with interferon-alpha is currently being explored and may result in prolongation of disease-free and, possibly also, overall survival. In both high- and low-grade lymphomas, intensification of therapy by myeloablative chemotherapy or combined chemoradiotherapy followed by autologous bone marrow transplantation (ABMT) or peripheral stem cell transplantation provides a promising and potentially curative prospective. In addition, new cytostatic agents such as the purine analogues--fludarabine, chlorodeoxyadenosine and deoxycoformycin--enlarge the therapeutic spectrum. More experimental approaches consist of the application of immunotoxins or radioisotypes, coupled to monoclonal antibodies directed against lymphoma-specific antigens. Overall, the substantial advances that have been achieved in the understanding of the biology and pathogenesis of malignant lymphomas, as well as the current achievements of therapy and the new promising perspectives, justify the hope that curative therapy can soon be offered to an increasing proportion of patients with NHL.

PMID: 8652232 [PubMed - indexed for MEDLINE]

CA Cancer J Clin. 1997 Nov-Dec;47(6):351-72.

Non-Hodgkin's lymphomas: current classification and management.

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Considerable progress has been made in the classification of non-Hodgkin's lymphomas during the past 15 years, and the use of specific monoclonal antibodies directed against cell surface antigens has contributed to the understanding of the immunology of the disease. Early-stage indolent lymphoma is treated with radiotherapy; treatment of advanced-stage indolent lymphoma varies. Aggressive lymphomas are treated with combination chemotherapy with or without regional radiotherapy, and highly aggressive lymphomas are treated with regimens similar to those for children with leukemia.

PMID: 9371057 [PubMed - indexed for MEDLINE]

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1. Quality of Life in Low-Grade Non-Hodgkin's Lymphoma

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Low-grade non-Hodgkin's lymphoma (NHL) is an indolent form of the disease with a generally slow course of progression. Although still usually incurable, low-grade disease has shown responsiveness to some of the newer chemotherapeutic and nonchemotherapeutic treatment options. However, since cure remains elusive, and since many patients with low-grade NHL may have few or even no symptoms initially, the decision about whether or not to initiate treatment logically must include quality-of-life (QOL) issues. This paper summarizes clinical and diagnostic characteristics of low-grade NHL that have some bearing on QOL considerations. Adverse effects of the more common treatment approaches are discussed according to their QOL implications, illustrating the relevance of QOL to the clinical management of low-grade disease. Finally, data from an ongoing study using the Functional Assessment of Cancer Therapy (FACT) measurement system are presented. These data offer a basis for comparing the QOL of patients with NHL to

that of individuals with other solid tumors, and also illustrate the effects of chemotherapy on QOL.[ONCOLOGY 12(5): 697-717, 1998]

In 1997, an estimated 54,000 people in the United States were diagnosed with non-Hodgkin's lymphoma (NHL).[1] This disease thus accounted for nearly 4% of cancer incidence overall.[1] In the same year (1997), almost 24,000 people died of the disease.[1]

The subclassification of low-grade NHL constitutes approximately 25% of all cases.[2] Incidence of low-grade disease is higher in people between the ages of 35 and 64 years (37%) than in those under age 35 (16%).[3] Ironically termed the "favorable" or indolent form of NHL due to a natural history characterized by slow disease progression and a relatively long duration of survival (7 to 10 years)[4] when compared to intermediate- and high-grade disease, low-grade NHL is still regarded as essentially incurable.[5,6]

The addition of new treatment options, a better understanding of factors that predict response, and the introduction of new nonchemotherapeutic therapies have improved the clinical management of low-grade NHL. These improvements have not yet produced a significant increase in cure rate, however.[7-9] For this reason, and because life-extending treatments produce toxicity and added cost, quality of life (QOL) emerges as a very relevant consideration when judging therapeutic benefit.

The course of progressive low-grade NHL is typified by sequential remissions and relapses, disease dissemination, and eventual resistance to current treatment approaches.[6] Also, since patients often opt for alternative treatments at times of relapse, they are likely to endure acute and chronic treatment toxicity, as well as psychosocial sequelae associated with chronic, life-threatening disease.

In summary, given that the disease produces symptoms, the chance for cure is low, and available treatments have a questionable impact on survival and known toxicity (or cost), QOL may be the most important clinical management concern. To date, however, there has been a paucity of relevant literature and research on the quality of life of patients with low-grade lymphoma, and no published randomized clinical trial has included QOL evaluation as an outcome. The need for reliable, valid measures of the physical, functional, emotional, and social impact of lymphoma is apparent. Although questionnaires that measure general QOL are available,[10-12] there is no lymphoma-specific QOL questionnaire or subscale that addresses the particular symptoms or concerns of patients with lymphoma or the effects of lymphoma treatments on life quality. Treatment decision-making (by both patient and physician) and practice guidelines would be enhanced by the ability to balance QOL consequences against the known benefits and drawbacks of established and investigational treatments, such as extension of survival time, durability of remission, toxicity of treatment, and effectiveness of palliation.

This paper will summarize the clinical characteristics of low-grade NHL, including classification, staging, and symptoms, as well as the predictors of treatment response. Adverse effects of the most common treatments and their QOL implications will also be discussed, in an attempt to illustrate the high degree of relevance of QOL considerations to clinical management. In addition, the psychosocial sequelae of NHL will be reviewed. Finally, data derived from a commonly used questionnaire, the Functional Assessment of Cancer Therapy (FACT) measurement system,[10] will be presented. These data were used to compare the QOL of patients with NHL to a matched sample of patients with mixed cancer types and a smaller sample of patients with Hodgkin's disease; the QOL of NHL patients according to treatment status (on vs off chemotherapy) were also compared.

2. Clinical Characteristics

Classification and Staging

Non-Hodgkin's lymphomas comprise a wide range of malignancies that originate in the lymphoid system. They differ according to their pathologic and immunologic characteristics and their prognostic classification.[3,5,6] Efforts have been made to create a taxonomy that effectively groups all lymphomas into distinct categories according to their morphology, course, and outcome. Due to the variability of lymphomas, however, development of a pure classification system still remains challenging.[6]

At present, NHLs are commonly classified by the International Working Formulation, established in 1982 by a special task force of the National Cancer Institute to consolidate lymphomas by clinically useful criteria so as to predict biological behavior, curability, and survival.[13] Another classification system, the revised European-American classification of lymphoid neoplasms (REAL) has been proposed but is not universally accepted.[14] Precise diagnostic evaluation of the histologic subtype and classification have become critical for appropriate management of the disease.[6]

The International Working Formulation defines three general categories of lymphomas—low grade, intermediate grade, and high grade—which are differentiated most notably by their aggressiveness or "malignant potential."[5] Low-grade lymphomas include small lymphocytic; follicular, small cleaved cell; and follicular, mixed, small cleaved and large cell subtypes, which are indolent by nature and initially responsive to a variety of treatments but eventually prove nonresponsive.[6]

Non Hodgkin's lymphoma is clinically staged using the Ann Arbor staging classification (stage I, II, III, IV), which indicates the extent to which lymph node regions and extralymphatic sites are involved.[15]

An unusual increase in the incidence of NHL since the 1970s,[5] combined with little improvement in relative survival rates, continues to challenge the medical community,[1] despite the availability of diverse treatment options. Risk factors associated with low-grade lymphomas include increasing age, male gender, exposure to chemotherapy and

radiation, and chronic immunosuppression.[3,5] Of particular importance to QOL are practice guidelines based on poor prognostic factors, such as age.

Diagnosis
Diagnostic procedures to determine the type of lymphoma and extent of disease are quite extensive, and often require that patients undergo a variety of invasive and noninvasive tests, procedures, and surgical explorations. Physical examination, peripheral lymph node biopsies, chest x-rays, computed tomographic (CT) scans, bilateral bone marrow biopsy, spinal taps, blood tests, and surgical evaluation of tissue and organ involvement collectively lead to an accurate diagnosis.[3,5]

Repeat assessments are necessary to determine response to treatment and guide therapeutic decisions. Chronic invasive assessments in patients with hematologic malignancies cause discomfort and are associated with heightened anxiety, especially at follow-up visits, where fear of recurrence may be confirmed.[16]

Symptoms
Disease symptoms include both common lymphoma symptoms that are indicative of active disease and specific symptoms highly influenced by the location(s) and extent of disease dissemination.[5] The majority of patients present initially with asymptomatic adenopathy (lymph node swelling) and may have active disease without symptoms for up to 3 years after diagnosis, making early treatment (for some) optional.[17] The indolent nature of the low-grade subtypes may also allow some patients to live a relatively prolonged symptom-free and active life until the disease progresses.

Nonspecific lymphoma symptoms, commonly referred to as B symptoms, include fatigue, fever, weight loss, and drenching night sweats. These symptoms are prognostically unfavorable and therefore are often an indication for treatment.[18] Other relevant symptoms include pain and cosmetic problems due to enlarged lymph nodes.

Independent of prognostic differences, treatment of symptomatic disease is more easily justifiable than treatment of asymptomatic disease, on QOL grounds. This will be addressed below.

Site-specific involvement can be limited or widespread, can occur anywhere in the lymphatic system (eg, lymph nodes, spleen, and bone marrow), and can spread to one or more extralymphatic organs (eg, stomach, intestine, bone, skin, oral cavity, and pharynx).[3,5] The presence of bulky masses causes discomfort and often pain.

Other symptoms vary and may include abdominal pain, ulcers, or bleeding if the gastrointestinal (GI) tract is involved.[5] If there is throat or sinus involvement, head and neck discomfort, throat pain, or swallowing difficulty can occur.[5] Patients with neurologic or musculoskeletal system involvement may experience neurologic and musculoskeletal pain and muscle weakness. With bone marrow involvement, weakened immunity or chronic infections can develop.[3]

In short, the range of possible symptoms and functional problems associated with low-grade NHL is diverse, and depends on the site and degree of involvement. Progressive disease dissemination to additional sites places patients at increased risk for new symptoms and problems, which are often unpredictable, although manageable with palliative therapies.

3. Predictors of Treatment Response and Survival

A great deal of attention has focused on evaluating predictors of treatment response and overall survival in order to optimize treatment selection.[18-22] Histologic subtype, disease stage, prior treatment, and age are often cited as determinants of treatment selection.[7,23,24] The presence of B symptoms, age greater than 65 years, poor performance status, high serum lactic dehydrogenase (LDH) levels, number of nodes involved, number of sites involved, intraabdominal involvement, immunoglobulin level, advanced (stage III/IV) disease, and histologic transformation to intermediate- or high-grade disease have been identified as factors that adversely affect survival.[18-22] These factors may also have important QOL implications, especially if they contribute to a significant decrease in physical well-being and functioning or preclude further treatment.

Histologic transformation to intermediate- or high-grade lymphoma has been observed in the natural course of untreated lymphoma and in patients who have received prior therapy.[17] Generally, transformation to higher-grade disease is an unfavorable sign, although there is a subset of patients who have responded well to additional therapy and have enjoyed relatively long-term survival.[25] Fear of histologic transformation (increasing aggressiveness and potential fatality of the disease) is an uncertainty that many patients with low-grade lymphoma must face.

In addition, the risk of developing a second malignancy has been shown to be higher (21%) in long-term NHL survivors (3 to 20 years), as compared with the estimated cumulative risk in the general population (15%).[26] This increased risk is believed to be related, in part, to immunosuppression and exposure to radiation therapy and chemotherapy.[25]

4. Treatment Options

Treatment of low-grade lymphoma continues to challenge physicians, who essentially are managing a chronic, incurable disease over many years. With the exception of some patients with localized stage I lymphomas treated with radiation and some stage II patients treated with combined chemotherapy and radiation, to date there is little evidence confirming that the type of treatment administered has a significant bearing on overall survival.[9,27] In addition, the advantages of early or aggressive treatment and its impact on overall survival have not been clearly demonstrated.[28,29] However, several treatment options are available with varying toxicity and QOL trade-offs: radiation therapy, alone or combined with chemotherapy, single-agent chemotherapy (oral and injectable), combination chemotherapies, bone marrow transplantation (BMT), monoclonal antibodies, and maintenance therapies.

QOL Implications
Standard treatment guidelines for low-grade lymphomas have been difficult to create given the diversity and relative safety and efficacy of available treatments, the wide range of currently identified prognostic factors, and the opportunity for participation in new clinical trials.[7] Although patients may benefit from many therapies, selecting optimal treatment approaches throughout the course of the disease can involve risks (perceived and actual) and trade-offs. For example, patients whose lymphoma is not treated initially may feel uneasy about not actively fighting the disease. Conversely, patients who pursue initial aggressive treatment may endure debilitating, even life-threatening side effects with long-term QOL consequences for an unknown potential advantage.

The lack of clinical trial data on QOL creates obstacles to deciding among various treatment options, especially with regard to early or aggressive therapies that have not been shown to benefit the traditionally most important outcome (overall survival). The degree to which patients are involved in this decision-making process is unclear, and probably depends somewhat on patient attitude and pursuit of information, as well as physician approach, ability, and interest in summarizing and communicating information about the trade-offs between treatment toxicities and probability of benefit. Although it is often helpful for patients to research and learn about their disease and exercise control over treatment choices, repeated involvement and informed consent to treatments that essentially involve a progressive gamble can be emotionally burdensome.[16]

Watchful Waiting vs Active Treatment—The "watch-and-wait" approach established by the Stanford group in the early 1980s[17] is a conservative approach to the treatment of a select group of patients with newly diagnosed low-grade NHL. Investigators have shown that watchful waiting for disease progression or symptoms before initiating therapy does not adversely affect overall survival.[17] For some patients, a high level of physical and functional QOL may be maintained for 3 or more years due to the fact that they are asymptomatic, may have spontaneous disease regression, and are not subject to the toxicities of induction or maintenance therapies.[17] However, because these clinically logical conclusions were not demonstrated with formal QOL assessment, little is known about the emotional and social well-being of patients who defer treatment.

Quality-of-life implications for patients receiving active treatment depend, in part, on the type of therapy, method and frequency of delivery, and the availability and use of supportive agents to counter side effects. Frequently, chemotherapy for NHL is myelotoxic, compromising an already deficient immune system. The addition of radiation therapy, other alkylating agents, or biological response modifiers can significantly contribute to the problem. For example, the combination of chemotherapy and total-body irradiation may lead to acute bone marrow suppression,[30] and the addition of interferon to chemotherapy may result in debilitating side effects, such as fatigue.[31]

Because there are no formal QOL data from randomized clinical trials of low-grade lymphoma patients, we can only estimate the impact of previously studied treatments on QOL by treating toxicity data as a proxy for QOL assessment. Naturally, this must be done with caution because the provider is the source of toxicity data, whereas the patient

is the source of QOL data. Also, toxicity data cover only *some* of the treatment-related QOL problems that patients can have.

Radiation Therapy
Radiation therapy has been shown to produce significant, possibly curative results in a subgroup of patients with early-stage (I or II) localized low-grade lymphoma.[27] Except for palliative reduction of bulky disease, radiation therapy is not commonly used in the management of advanced disease. Localized radiotherapy (involved-field, extended-field, or total lymphoid irradiation) usually does not yield serious toxicities. Skin sensitivity and dryness are common problems at local sites.[32]

When combined with chemotherapy in any stage of disease, radiation therapy may cause pneumonitis, myocardial toxicity,[30] side effects specific to the radiation site,[32] gonadal dysfunction, and sterility.[33] When radiation therapy is used for palliative reduction of bulky disease, its value can be understood as a trade-off between symptomatic relief and treatment toxicity, since survival is not altered.

Chemotherapy

Both single chemotherapeutic agents and multidrug combinations have been used in the treatment of low-grade NHL.

Single Agents—Single-agent therapies, such as chlorambucil (Leukeran) and cyclophosphamide (Cytoxan, Neosar), have been shown to yield similar responses to more aggressive multidrug regimens in their impact on overall survival and are generally less toxic.[34,35] In clinical trials of each drug, most patients experienced treatment-related toxicities, including nausea/vomiting/anorexia and/or diarrhea (31%),[35] GI symptoms (90%),[34] and leukopenia (58% with cyclophosphamide[34] and 67% with chlorambucil[35]). Thrombocytopenia (43%) was reported with chlorambucil,[35] while hemorrhagic cystitis (37%) and alopecia (26%) were observed with cyclophosphamide.[34]

Combination regimens—such as CVP (cyclophosphamide, vincristine [Oncovin], and prednisone) and CHOP (cyclophosphamide, doxorubicin, Oncovin, and prednisone) often produce more toxic effects, and are accompanied by questionable trade-offs. For example, aggressive front-line treatment does not extend overall survival but has been shown to induce a more rapid response, higher response rate, and longer freedom from disease progression.[28,29,36] Data from trials of CHOP report major hematologic and neurotoxic effects, however, as well as death secondary to therapy.[37,38] Two clinical trials reported fatal toxicities in 1%[37] and 3%[38] of patients and grade 3 or 4 toxicities in 28%[38] and 31%[37]. In other trials, common side effects of CHOP included leukopenia (89% grade 3 or 4), thrombocytopenia (11% grade 3), and anemia (74% grade 3). Neutropenic fevers were common and often led to hospitalization (47%).[39]

Low sperm count and increased risk of infertility in men have also been shown to be consequences of combination chemotherapy.[40] The combination of cisplatin (Platinol)

and etoposide yielded serious toxicities when administered to 51 patients; these included hematologic toxicity (39% neutropenia, 35% thrombocytopenia, 16% anemia), severe hemorrhage,[3] and one death due to infection.[41]

Newer aggressive multidrug regimens used in patients with relapsed low-grade lymphoma, such as FMD (fludarabine, mitoxantrone, and dexamethasone) and DHAP (dexamethasone, Ara-C, and Platinol), have been shown to cause severe myelosuppression and secondary opportunistic infections (such as herpes zoster and *Pneumocystis* infections), bacterial and fungal infections, renal insufficiency, mucositis, and neurologic toxicity.[42,43] Some of these treatments have yielded higher response rates than traditional salvage therapies, but not without cost, functional impairment, and life-threatening toxicity.

Purine Analogs—The relatively new purine analogs have shown promise in low-grade lymphoma and thus provide additional options and challenges for the management of this disease.[44] Fludarabine (Fludara), 2'-deoxycoformycin (pentostatin [Nipent]), and 2-chlorodeoxyadenosine (2-CDA, cladribine [Leustatin]) have demonstrated single-agent antitumor activity, with documented partial and complete response rates and prolonged remissions.[45,46]

The frequency and degree of toxicity reported vary by trial but are consistent with the hematologic side effects of other chemotherapies, and include lymphopenia, leukopenia, neutropenia, thrombocytopenia, opportunistic infections, bacterial and fungal infections, nausea, diarrhea, and peripheral neuropathy.[46-48] Infection-related deaths secondary to treatment have been documented with both fludarabine and cladribine.[48-50] One recent study suggested that dose reductions of standard cladribine treatment can afford patients similar results without the severity of myelotoxicity and infection risk that accompany elevated dose—a meaningful QOL consideration.[51]

The purine analogs are important additions to the spectrum of treatment options. These agents have received a great deal of attention recently due not only to their value as effective anticancer drugs but also to their ability to invoke remissions in previously treated and older patients.[47]

Bone Marrow Transplantation

Interest in evaluating the success of autologous and allogeneic BMT for patients with low-grade lymphoma has paralleled advances in the science of stem-cell transplantation. As is true for most other available treatments, stem-cell transplantation has been shown to prolong failure-free survival, but more mature data are needed to demonstrate any overall survival advantage or curative effect.[52-56] Severe, life-threatening toxicities of myeloablative chemotherapy and radiation therapy are considerable. In one retrospective review of low-grade lymphoma patients, 8% died within 100 days of transplantation.[56]

The QOL consequence of BMT have been studied in patients with mixed cancers (including those with NHL). Although many patients have a good recovery from BMT, the period of convalescence is protracted and may include a prolonged hospital stay in

isolation. This can precipitate long-term physical and functional problems. Treatments can also cause gonadal damage and infertility (with their attendant consequences for psychosocial and sexual functioning).[33]

In one study of allogeneic transplantation, 40% of recipients took more than 1 year to return to normal physical and psychosocial functioning and employment status.[57] Another study of patients receiving an allogeneic or autologous transplant demonstrated that a majority of patients experienced physical difficulties (weakness and fatigue), as well as sexual and occupational problems, at more than 12 months post-BMT.[58]

Without demonstrated cure, treatments as intensive as BMT pose a compelling QOL trade-off challenge to low-grade lymphoma patients and their providers with regard to making treatment decisions.

Monoclonal Antibodies
New treatment approaches for low-grade lymphoma include monoclonal antibodies that attach to receptors found on B-lymphocytes. One general approach uses radiolabeled antibodies; another uses a "naked" antibody. Preliminary studies of these monoclonal antibodies as single agents has demonstrated encouraging response rates and some evidence of long-term disease control, but the median duration of response and impact on overall survival are still unknown.[59]

The most frequently observed side effects of monoclonal antibody therapy occur during the infusion and include rigor, fever, chills, nausea, headaches, and hypotension.[60,61] The infusion-related side effects typically diminish in severity with repeated administration.[60,61] Other toxicities include myelosuppression and infections, which occur at a lower rate with naked antibodies than with radiolabeled antibodies.[60,61]

Given the available spectrum of chemotherapy regimens and their toxicities, treatments that have limited and non-life-threatening toxicities, such as monoclonal antibodies, may be relatively more favorable to the QOL of patients who endure repeated treatments and relapses.

Maintenance Therapies
Maintenance therapies are also used in the treatment of low-grade lymphoma, and are believed to contribute to the prolongation of relapse-free survival—a meaningful end point given the incurability of the disease.[62,63] Maintenance therapies, such as interferon- alfa-2a (Roferon-A) or interferon-alfa-2b (Intron A) and intermittent CVP, have yielded mixed results with regard to their value and efficacy. Although progression-free survival advantages have been demonstrated, the trade-off of chronic side effects makes the decision of whether to use maintenance therapy a difficult one.

Leukopenia, thrombocytopenia, anemia, vomiting, and neurologic effects were seen in one trial of CVP.[62] Some patients (14%) withdrew from the study and an additional 14% refused further treatment because of side effects.[62]

Interferon as maintenance therapy has also had varied results but is known to cause debilitating fatigue and other flu-like symptoms, which may be of severe consequence to physical well-being and role functioning.[64,65] One study of multiple myeloma patients who received interferon therapy demonstrated that side effects had negative QOL consequences (ie, fatigue and fever had a negative impact on functioning), but for a subgroup of patients, the decrease in life quality was worth even a small survival or disease-free survival benefit.[31]

This finding provides a good argument for the value of further QOL research for treatments (such as interferon) complicated by trade-offs that may vary according to patient preferences. The integration of QOL data and patient preferences, combined with the evaluation of trade-offs, such as with the Quality-Adjusted Time Without Symptoms or Toxicity (Q-TWiST) statistical technique, may further guide the choice of optimal treatment. The concept of a "symptom-free interval," if developed within the Q-TWiST methodology to include patients with active, essentially asymptomatic disease, could help move this effort forward.

Overall, balancing treatment efficacy and toxicity is important in determining its value. When cure is unlikely or impossible, extending life becomes a valued goal. A treatment that extends life without improving its quality relative to a no-treatment alternative becomes increasingly less valuable as treatment toxicity becomes increasingly more significant.

5. Psychosocial Sequelae of NHL

A great deal of literature is available on the QOL and psychosocial experience of cancer treatment and survivorship, but little pertains specifically to low-grade lymphoma. Hodgkin's disease has offered investigators a unique opportunity to study QOL and long-term psychosocial adaptation of a group of patients in which the cure rate approaches 90%.[66,67] Quality-of-life research on other tumors, such as lung cancer, provides important information about treatment differences and may have value as a predictive indicator of survival and response to therapy.[68] It has been suggested that this information can be incorporated into practice guidelines to help guide decisions about whether to continue aggressive therapy or switch to palliative care.[68] Patients with low-grade lymphoma are at risk of undergoing repeated aggressive and experimental treatment approaches with questionable trade-offs, may live for protracted periods of time as "survivors" (free of disease), are likely to experience difficulties in psychosocial adaptation to illness and to long-term survivorship, and must contend with the uncertainty of relapses and essential incurability of the disease.

QOL Concerns of Patients With Hematologic Cancers

Lesko[16] has comprehensively reviewed the QOL concerns of patients with hematologic malignancies, including issues common to the cancer experience and those specific to leukemia and lymphoma. Due to the potential fatality of the disease and prolonged, complicated treatment approaches, these patients have heightened concern about issues of death, dependence, disfigurement, disruption, and disability. Other significant concerns

related to living with uncertainty and the "emotional exhaustion" due to the potential long-term clinical course of the disease, financial burden, increased risk for depressive mood and anxiety, and family disruption.

Long-term survival issues included conditioned nausea and vomiting, medical concerns (long-term and late effects of treatment), and psychological concerns, such as fear of recurrence and abandoning the role of patient. Conditioned nausea and vomiting, for example, have been shown to extend 7 to 12 years beyond treatment in patients with Hodgkin's disease.[69]

Anxiety and Depression—Other research has demonstrated the prevalence of depression and anxiety in mixed lymphoma patients.[70-72] In one study of the prevalence of psychological distress in 2,388 patients with various types of cancer (breast, lung, colon, head and neck, gynecologic, prostate, and brain cancers, lymphoma, hepatoma), lymphoma patients scored highest for depression.[70]

A high level of anxiety and depressive symptoms or illness (49%) was also found in a group of 98 patients with Hodgkin's disease or NHL.[72] Mood disturbance was associated with negative treatment effects (particularly pain and changes in appetite and taste). Common adverse effects of treatment included hair loss, vomiting, nausea, and loss of appetite. Quality-of-life effects of treatment-related emesis impaired the ability of some patients to complete tasks, work, care for themselves, perform normal daily activities, and enjoy social activities and meals. Following treatment, a subgroup of patients continued to experience a lack of energy, loss of libido, irritability, tiredness, and thinking/memory handicaps. Impairments in social adaptation were less well-defined, although patients reported problems or long-term delays in returning to work.[72]

Symptoms of depression and anxiety over the impact of disease on health and life expectancy predominated in 40 mixed lymphoma patients.[73] Psychological status did not change significantly over the course of early treatment,[73] although other evidence has suggested that psychological symptoms at diagnosis are more severe than at 4 months post-diagnosis.[74] Psychological adaptation in patients with chronic illness may be pivotal to coping with the physical, emotional, social, and functional disrup-tions caused by cancer, including lymphoma.[74,75]

Uncertainty about the illness— has been cited as a psychosocial issue in patients with hematologic malignancies.[76] Unfortunately, available data relate to other diseases. One study of women with gynecologic cancers suggests that uncertainty about the illness-wellness state is predictive of some health-related QOL scores.[77] Low-grade lymphoma patients may be at high risk for the negative implications of uncertainty, and may benefit from research evaluating the impact of uncertainty in illness, as well the value of implementing interventions designed to help patients cope with uncertainty and fear of recurrence or progression.

In a group of 40 mixed cancer patients (including lymphoma patients), the negative impact of cancer recurrence has been shown to be considerable, often distinguished as

being more traumatic than the initial diagnosis.[78] Risk of emotional trauma at points of recurrence are likely to be substantial in patients with low-grade lymphoma. Loss of control (physical and psychologically based), feelings of grief and anger, presence of chronic fatigue, and other long-term and late effects (such as permanent central nervous system damage and infertility), altered self-esteem and self-image, difficulties with resumption of prediagnosis roles, somatic fixation at disease-free intervals, employment and insurance discrimination, and family disruption have also been addressed,[16,76,79-81] but deserve further attention. Table 1 lists the major QOL issues that may concern patients with low-grade lymphoma.

Positive Adaptation to Illness—Low-grade lymphoma patients may suffer diverse treatment and psychosocial consequences, with a select group able to live a relatively healthy and active lifestyle for a considerable time following diagnosis. Some patients will be exposed to aggressive and experimental therapies, while others, especially the elderly, may endure a less toxic, less debilitating course of treatment.

Psychosocial adaptation to illness and survival seem to be highly influenced by a host of variables and, therefore, are likely to vary from patient to patient. Positive aspects of living with chronic or terminal illness have been documented and should not be overlooked in this population. Social, family, and emotional domains have been shown to be positively influenced by life-threatening illness.[75,82] The ability to find meaning in illness, "dispositional optimism," and hope are thought to mediate this effect.[82] Patients may report an increased awareness and enjoyment of "life in the moment" or find value in such things as the coping skills developed by children who have lived with a parent who has a chronic illness or who have faced parental loss.[83]

6. QOL Evaluation of Patients With NHL

An understanding of the overall QOL of people with NHL can be achieved by combining the medical/physical aspects of the disease (described earlier) with its psychosocial sequelae. Taken together, the physical, functional, psychological, and social impact of NHL and its treatment can be evaluated using one of the currently available QOL questionnaires created for people living with cancer. One such questionnaire, the Functional Assessment of Cancer Therapy-General (FACT-G),[10] has been administered in an ongoing study to over 1,000 cancer patients, many of whom have NHL. Some of these data will be presented below.

NHL Patients Compared to Other Cancer Patients

Table 2 presents QOL (FACT-G) data from a mixed sample of 141 patients (inpatients and outpatients) with NHL. These patients represent a subset of a larger sample of 1,196 patients with mixed cancers from five institutions (Rush-Presbyterian-St. Luke's Medical Center, Northwestern University, Medical College of Ohio, Fox Chase Cancer Center, and Johns Hopkins Oncology Center). The mean FACT-G scores are quite comparable to those of the original standardization sample.[10]

To allow a direct comparison of FACT subscale scores between NHL patients and patients with general solid tumors from the same study, an age- and gender-matched group of 141 general cancer patients was extracted. This comparison showed no significant differences on any of the FACT subscales, suggesting that the QOL of NHL patients is generally comparable to that of patients with other cancers.

To examine the comparability of patients with NHL to patients with other lymphomas (ie, Hodgkin's disease), a subset of 32 NHL patients, again matched for age and gender to the existing set of 32 Hodgkin's disease patients, was extracted. This comparison, unlike the previous one, showed that the NHL patients reported significantly lower physical and functional well-being than the Hodgkin's disease patients (see Table 3). These lower scores resulted in decreased FACT-G (total QOL) scores as well.

To follow up on this difference, a multiple regression analysis was conducted on the matched groups, entering five predictors of FACT physical well-being and functional well-being scores: diagnosis; Eastern Cooperative Oncology Group (ECOG) performance status; stage of disease; current radiotherapy; and current chemotherapy. The purpose of this analysis was to help determine the extent to which each of these variables contributes to the decline in QOL seen among NHL patients (Table 4). For this reason, all of the factors were entered simultaneously using a stepwise approach, followed by relevant analysis of covariance to confirm unique explanatory ability where noted.

In the first (physical well-being) model, performance status and current chemotherapy were both strongly predictive of physical well-being score, with the five-variable model explaining 48% of its variance. Interestingly, diagnosis itself and stage of disease were not significant factors. Current radiotherapy may have been a nonfactor due to the very low number of patients currently receiving that mode of therapy (5 out of 64). In the second (functional well-being) model, only diagnosis (Hodgkin's disease vs NHL) was predictive of functional well-being score, and the predictive ability was weak overall, explaining only 17% of its variance.

The wording of items in each of the subscales (Table 5) may shed some light on why physical well-being scores were so much more responsive to the effects of chemotherapy. First, all of the items in the physical well-being questionnaire are negatively worded, reflecting the perceived physical state. In contrast, the functional well-being questions are positively worded and emphasize functional ability, which may be less directly and less strongly compromised compared to physical symptoms. A second possible reason is that the physical well-being subscale specifically asks about treatment side effects.

In any event, it is clear from Table 4 not only that physical well-being is very strongly related to performance status but also that, independent of this

relationship, the physical well-being component of QOL is worsened by chemotherapy. This appears to be a more salient factor than age, gender, or actual type of lymphoma (Hodgkin's disease vs NHL).

NHL Patients Who Did and Did Not Receive Chemotherapy

This observation led us back to our original complete set of 141 NHL patients, which we divided into those who received chemotherapy vs those did not (Table 6). A comparison of these two groups showed that patients receiving chemotherapy showed significantly lower physical, emotional, and functional well-being, as well as lower total QOL scores. These differences, presented in Table 6 as unadjusted mean differences for the sake of easy comparison to other samples of patients, remained statistically significant after adjustments were made for other covariates (age, gender, performance status, and stage of disease).

These data provide some empirical support for something that is obvious to most clinicians; namely, that in the absence of a possible direct benefit on disease symptoms, chemotherapy is detrimental to short-term QOL. More importantly, these data provide a basis for comparison to other patient groups, and evidence that the QOL metric produced by the FACT can produce useful, responsive scores in this population. This is not to say that a lymphoma-specific subscale would not be a useful complement to the FACT-G, particularly for the purpose of obtaining lymphoma-specific information related to B symptoms, unique treatment concerns, and strategies for coping with a chronic disease. Such a subscale probably would add a dimension of sensitivity to the assessment.

Comparison of Two Groups Receiving Chemotherapy

As an illustration of how these data, as described, can be used in comparisons with other patient samples, we drew data from a different study of mixed cancer patients (227 of whom had NHL and 46, Hodgkin's disease; sample 2 in Table 7). The purpose of this analysis was not to make a direct statistical comparison between the groups, but rather, to present scores side-by-side to allow rough comparisons to be made. This sample of patients was drawn from a community phase IV trial of epoetin alfa (Epogen, Procrit) for the treatment of anemia related to chemotherapy. All of these patients were, therefore, receiving chemotherapy and had hemoglobin levels below 11 g/dL. Thus, the group of 80 NHL patients receiving chemotherapy from Table 6 would provide a useful comparison (sample 1 in Table 7).

Visual comparison of the NHL patients in sample 1 and sample 2 reveals strikingly similar unadjusted mean scores. On the other hand, the sample 2 NHL patients appear to have higher QOL than the sample 2 Hodgkin's disease patients, in contrast to the sample 1 data presented earlier. However, these differences are not significant after the effects of age and gender are removed.

It has commonly been observed that, under conditions of similar objective health data, older patients tend to report better emotional and even physical well-being. This highlights the importance of considering nondisease factors when comparing QOL data across samples. It is not at all unusual to find that, although different diseases have very unique natural histories, symptoms, and treatment considerations, the QOL considerations and differences may be more strongly related to such factors as age and whether or not the patient is currently receiving treatment.

7. Conclusions

Taken as a whole, the data presented here support a long-held clinical notion about NHL: Given the questionable survival benefit of most treatment options, and given the known adverse impact of chemotherapy on QOL, it seems prudent to manage patients with less aggressive approaches when possible. The presence or absence of disease symptoms is often the determining factor when deciding about treatment, with treatment more likely when symptoms are present. It appears reasonable to conclude that the adverse effects of toxic treatments (ie, cytotoxic chemotherapy) are not easily offset by improvements in clinical outcome or the emotional advantages of receiving treatment, although this conclusion is based on observational data in uncontrolled clinical settings. Therefore, a watch-and-wait or minimally toxic approach to the managements of some patients with low-grade NHL seems to be well-justified. Of course, patient values and preferences for aggressive therapy must be factored into this general equation.

8. References

1. Parker SL, Tong T, Bolden S, et al: Cancer statistics, 1997. CA Cancer J Clin 47(1):5-27, 1997.

2. Aviles A, Talavera A, Guzman R, et al: Treatment of refractory low-grade lymphoma with chlorambucil alternating with interferon and radiotherapy. Cancer Biother 10(4):273-277, 1995.

3. Molina A, Pezner RD: Non-Hodgkin's lymphoma, in Pazdur R, Coia LR, Hoskins WJ, et al (eds): Cancer Management: A Multidisciplinary Approach, 2nd ed, pp 239-269. Huntington, New York, PRR, 1997.

4. Weisdorf DJ, Anderson JW, Glick JH, et al: Survival after relapse of low-grade non-Hodgkin's lymphoma: Implications for marrow transplantation. J Clin Oncol 10(6):942-947, 1992.

5. Hardy R, Horning SJ: Lymphomas: non-Hodgkin's, in Dollinger M, Rosenbaum E, Cable G (eds): Everyone's Guide to Cancer Therapy, 2nd ed (revised), pp 492-500. Kansas City, Andrews & McMeel, 1994.

6. Stein R: A Chemotherapy of human cancer: Hodgkin's disease and malignant lymphomas, in Skeel RT, Lachant NA (eds): Handbook of Cancer Chemotherapy, 4th ed, pp 450-483. Boston, Little Brown, 1995.

7. Hagemeister FB: Low grade lymphomas: New entities and treatment concepts. Med Oncol 12(3):131-142, 1995.

8. Rosenberg SA: The low-grade non-Hodgkin's lymphomas: Challenges and opportunities. J Clin Oncol 3(3):299-310, 1985.

9. Vose JM: Classification and clinical course of low-grade non-Hodgkin's lymphomas with overview of therapy. Ann Oncol 7(suppl):S13-19, 1996.

10. Cella DF, Tulsky DS, Gray G, et al: The Functional Assessment of Cancer Therapy (FACT) scale: Development and validation of the general measure. J Clin Oncol 11(3):570-579, 1993.

11. Ware JE, Sherbourne CD: The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual framework and item selection. Med Care 30(6):473-483, 1992.

12. Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85(5):365-376, 1993.

13. Rosenberg S, Berard C, Brown J, et al: National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: Summary and description of a working formulation for clinical usage: The non-Hodgkin's lymphoma Pathologic Classification Project. Cancer 49:2112, 1982.

14. Harris NL, Jaffee ES, Stein H, et al: A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 84(5):1361-1392, 1994.

15. Carbone PP, Kaplan HS, Musshoff K, et al: Report on the committee on Hodgkin's disease staging classification. Cancer Res 31:1860-1861, 1971.

16. Lesko L: Hematological malignancies, in Holland HC, Rowland JH (eds): Handbook of Psychooncology: Psychological care of the patient with cancer, pp 218-231. New York, Oxford University Press, 1989.

17. Horning SJ, Rosenberg SA: The natural history of initially untreated low-grade non-Hodgkin's lymphomas. N Engl J Med 311(23):1471-1475, 1984.

18. Gallagher CJ, Gregory WM, Jones AE, et al: Follicular lymphoma: Prognostic factors for response and survival. J Clin Oncol 4(10):1470-1480, 1986.

19. Maksymiuk AW, Haines C, Tan LK, et al: Age-related prognostic factor analyis in non-Hodgkin's lymphoma. Can J Oncol 6(1):435-442, 1996.

20. Lopez-Guillermo A, Montserrat E, Bosch F, et al: Low-grade lymphoma: Clinical and prognostic studies in a series of 143 patients from a single institution. Leuk Lymphoma 15:159-165, 1994.

21. Morel P, Dupriez B, Plantier-Colcher I, et al: Long term outcome of follicular low-grade lymphoma: A report of 91 patients. Ann Hematol 66(6):303-308, 1993.

22. Parker D, Alison DL, Barnard DL, et al: Prognosis in low-grade non-Hodgkin's lymphoma: Relevance of the number of sites involved, absolute lymphocyte count and serum immunoglobulin level. Hematol Oncol 12:15-27, 1994.

23. Lichtman SM: Lymphoma in the older patient. Semin Oncol 22(1;suppl1):25-28, 1995.

24. Armitage JO: Treatment of non-Hodgkin's lymphoma. N Engl J Med 328(14):1023-1030, 1993.

25. Yuen AR, Kamel OW, Halpern J, et al: Long-term survival after histologic transformation of low-grade follicular lymphoma. J Clin Oncol 13(7):1726-1733, 1995.

26. Travis LB, Curtis RE, Glimelius B, et al: Second cancers among long-term survivors of non-Hodgkin's lymphoma. J Natl Cancer Inst 85(23):1932-1937, 1993.

27. MacManus MP, Hoppe RT: Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol 14(4):1282-1290, 1996.

28. Kimby E , Mellstedt H: Chlorambucil/prednisone (ChP) vs CHOP in symptomatic low-grade lymphomas. Fifth International Conference on Malignant Lymphoma, p 53. Lugano, Switzerland, June 9-12, 1993.

29. Dana BW, Dahlberg S, Nathwani BN, et al: Long-term follow-up of patients with low-grade lymphomas treated with doxorubicin-based chemotherapy or chemoimmunotherpay. J Clin Oncol 11(4):644-651, 1993.

30. Hoppe RT, Kushlan P, Kaplan HS, et al: The treatment of advanced stage favorable histology non-Hodgkin's lymphoma: A preliminary report of a randomized trial comparing single agent chemotherapy, combination chemotherapy, and whole body irradiation. Blood 58(3):592-598, 1981.

31. Cole B: Clinical benefits vs quality of life of patients receiving interferon. OncoLink Home Page, May 22, 1996. http://oncolink, upenn.edu

32. National Cancer Institute: Radiation and. You: A Guide To Self-Help During Treatment. NIH Publication no. 95-2227. Bethesda, Maryland, National Cancer Institute, revised October 1993.

33. Chatterjee R, Goldstone AH: Gonadal damage and effects of fertility in adult patients with hematological malignancy undergoing stem cell transplantation. Bone Marrow Transplant 17:5-11, 1996.

34. Mendelson D, Block J, Serpick A: Effect of large intermittent intravenous doses of cyclophosphamide in lymphoma. Cancer 25(3):715-720, 1970.

35. Kaung D, Wittington R, Spencer H, et al: Comparison of chlorambucil and streptonigrin (NSC-45393) in the treatment of malignant lymphomas. Cancer 23(6):1280-1283, 1969.

36. Rijlaarsdam J, Toonstra J, Meijer O, et al: Treatment of primary B-cell lymphomas of follicle center cell origin: A clinical follow-up of 55 patients treated with radiotherapy or polychemotherapy. J Clin Oncol 14(2):549-555, 1996.

37. Fisher R, Gaynor E, Dahlberg S, et al: Comparison of standard regimen CHOP with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 328(14):1002-1006, 1993.

38. Jones SE, Grozea PN, Miller TP, et al: Chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone alone or with levamisole or with levamisole plus BCG for malignant lymphoma: A Southwest Oncology Group study. J Clin Oncol 3(10):1318-1324, 1985.

39. Meyer R, Browman G, Samosh M, et al: Randomized phase II comparison of standard CHOP with weekly CHOP in elderly patients with non-Hodgkin's lymphoma. J Clin Oncol 13(9):2386-2393, 1995.

40. Pryzant RM, Meistrich ML, Wilson G, et al: Long-term reduction in sperm count after chemotherapy with and without radiation therapy for non-Hodgkin's lymphomas. J Clin Oncol 11(2):239-247, 1993.

41. Rybak ME, Anderson J, Kaplan R, et al: A phase II trial of etoposide and cisplatin in patients with refractory and relapsed non-Hodgkin's lymphoma: Cancer and Leukemia Group B study 8351. Med Pediatr Oncol 21:441-445, 1993.

42. McLaughlin P, Hagemeister FB, Romaguera JE, et al: Fludarabine, mitoxantrone, and dexamethasone: An effective new regimen for indolent lymphoma. J Clin Oncol (4):1262-1268, 1996.

43. Velasquez WS, Cabanillas F, Salvador P, et al: Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 71(1):117-122, 1988.

44. Pott-Hoeck C, Hiddemann W: Purine analogs in the treatment of low-grade lymphomas and chronic lymphocytic leukemia. Ann Oncol 6(5):421-433, 1995.

45. Piro LD: Cladribine in the treatment of low-grade NHL. Semin Hematol 33(1;suppl):34-39, 1996.

46. Morton J, Taylor K, Bunce I, et al: High response rates with short infusional 2-chlorodeoxyadenosine in de novo and relapsed low-grade lymphoma: Australian and New Zealand Study Group. Br J Haematol 95:110-115, 1996.

47. Hochster HS, Kim K, Green MD, et al: Activity of fludarabine in previously treated non-Hodgkin's low-grade lymphoma: Results of an Eastern Cooperative Oncology Group study. J Clin Oncol 10(1):28-32, 1992.

48. Rohatiner A, Foran J, Coiffier B, et al: Fludarabine in newly-diagnosed diffuse low-grade non-Hodgkin's lymphoma (abstract 1287). Proc Am Soc Clin Oncol 15:419, 1996.

49. Hoffman MA: Cladribine for the treatment of indolent non-Hodgkin's lymphoma. Semin Hematol 33(1;suppl 1):40-44, 1996.

50. Szelenyi H, Foss HD, Kreuser ED, et al: Fatal mucor pneumonia after treatment with 2-chlorodeoxyadenosine for non-Hodgkin's lymphoma. Ann Hematol 73(3):145-147, 1996.

51. Betticher DC, von Rohr A, Ratschiller D, et al: Fewer infections, but maintained anti-tumor activity with moderate vs standard dose cladribine (2-CDA) in pretreated patients with low grade non-Hodgkin's lymphoma (NHL) (abstract 56). Proc Am Soc Clin Oncol 16:16a, 1997.

52. Freedman AS, Gribben JG, Neuberg D, et al: High-dose therapy and autologous bone marrow transplantation in patients with follicular lymphoma during first remission. Blood 88(7):2780-2786, 1996.

53. Shouten IC, Raemaekers JJ, Kluin-Nelemans HC, et al: High dose therapy followed by bone marrow transplantation for relapsed follicular non-Hodgkin's lymphoma: Dutch HOVON Group. Ann Hematol 73(6):273-277, 1996.

54. Suki S, McLaughlin P, Przepiorka D, et al: The role of bone marrow transplantation (BMT) in 39 adult patients with low-grade non-Hodgkin's lymphoma (NHL) (abstract 1288). Proc Am Soc Clin Oncol 12:378, 1993.

55. Lazarus HM: Bone marrow transplantation in low-grade non-Hodgkin's lymphoma. Leuk Lymphoma 17:199-210, 1995.

56. Bierman PJ, Vose JM, Anderson JR, et al: High-dose therapy with autologous hematopoietic rescue for follicular low-grade non-Hodgkin's lymphoma. J Clin Oncol 15(2):445-450, 1997.

57. Syrjala KL, Chapko MK, Vitaliano PP, et al: Recovery after allogeneic marrow transplantation: Prospective study of predictors of long-term physical and psychosocial functioning. Bone Marrow Transplant 11:319-327, 1993.

58. Andrykowski MA, Greiner CB, Altmaler EM, et al: Quality of life following bone marrow transplantation: Findings from a multicentre study. Br J Cancer 71(6):1322-1329, 1995.

59. Davis TA, Maloney DG, Liles TM, et al: Long-term remissions in patients treated with anti-idiotype monoclonal antibodies for non-Hodgkin's lymphoma (abstract 1383). Proc Am Soc Clin Oncol 15:444, 1996.

60. McLaughlin P, Grillo-López AJ, Czuczman M, et al: IDEC-C2B8 (rituximab): Clinical activity in clinically chemoresistant (CCRD) low-grade or follicular lymphoma (LG/F NHL) and in patients relapsing after anthracycline therapy (Anthra-Rx) or ABMT (abstract 55). Proc Am Soc Clin Oncol 16:16a, 1997.

61. Tang SC, Hewitt HK, Bernstein NL: Objective clinical response in patients with recurrent low-grade lymphoma treated with CAMPATH-1H monoclonal antibody (abstract 1255). Proc Am Soc Clin Oncol 14:399, 1995.

62. Ezdinli EZ, Harrington DP, Kucuk O, et al: The effect of intensive intermittent maintenance therapy in advanced low-grade non-Hodgkin's lymphoma. Cancer 60(2):156-160, 1987.

63. Hagenbeek A, Carde P, Somers R, et al: Interferon-alfa-2a versus control as maintenance therapy for low-grade non-Hodgkin's lymphoma: Results from a prospective randomized clinical trial (abstract 1203). Proc Am Soc Clin Oncol 14:386, 1995.

64. Ludwig H, Fritz E, Neuda J, et al: Which risk/benefit tradeoffs would lead patients with myeloma to opt for interferon treatment? (abstract 40). Proc Am Soc Clin Oncol 16:12a, 1997.

65. McLaughlin P, Cabanillas F, Hagemeister FB, et al: CHOP-Bleo plus interferon for stage IV low-grade lymphoma. Ann Oncol 4(3):205-222, 1993.

66. Henry-Amar M: Hodgkin's disease: Treatment sequelae and quality of life. Baillieres Clinical Hematol 9(3):595-618, 1996.

67. Kornblith AB, Anderson J, Cella DF, et al: Hodgkin's disease survivors at increased risk for problems in psychosocial adaptation. Cancer 70(8):2214-2224, 1992.

68. Cella D, Fairclough DL, Bonomi PB, et al: Quality of life (QOL) in advanced non-small cell lung cancer (NSCLC): Results from Eastern Cooperative Oncology Group (ECOG) study E5592 (abstract 4). Proc Am Soc Clin Oncol 16:2a, 1997.

69. Cella DF, Pratt A, Holland JC: Persistent anticipatory nausea, vomiting, and anxiety in cured Hodgkin's disease patients after completion of chemotherapy. Am J Psychiatry 143:641-643, 1986.

70. Zabora JR, Brintzenhofcszoc KM, Smith ED: Prevalence of psychological distress by cancer site (abstract 1627). Proc Am Soc Clin Oncol 15:507, 1996.

71. Pettingale KW, Burgess C, Greer S: Psychological response to cancer diagnosis: I. Correlations with prognostic variables. J Psychosom Res 32(3):255-261, 1988.

72. Devlen J, Maguire P, Phillips P, et al: Psychological problems associated with diagnosis and treatment of lymphoma: I. Retrospective study. Br Med J 295:953-954, 1987.

73. Lloyd GG, Parker AC, Ludlam CA, et al: Emotional impact of diagnosis and early treatment of lymphomas. J Psychosom Res 28(2):157-162, 1984.

74. Cassileth BR, Lusk EJ, Strouse TB, et al: Psychosocial status in chronic illness: A comparative analysis of 6 diagnostic groups. N Engl J Med 311:506-511, 1984.

75. Taylor EJ: Whys and wherefores: Adult patient perspectives of the meaning of cancer. Semin Oncol Nurs 11:32-40, 1995.

76. Persson L, Hallberg IR: Acute leukemia and malignant lymphoma patients experience of disease, treatment, and nursing care during the active treatment phase: An explorative study. Eur J Cancer Care 4(3):133-142, 1995.

77. Padilla GV, Mishel MH, Grant MM: Uncertainty, appraisal and quality of life. Qual Life Res 1(3):155-165, 1992.

78. Cella DF, Mahon SM, Donovan, MI: Cancer recurrence as a traumatic event. Behav Med 16(1):15-22, 1990.

79. Harpham WS: After Cancer: A Guide to Your New Life. New York, WW Norton, 1994.

80. Wallwork L, Richardson A: Beyond cancer: Changes, problems and needs expressed by adult lymphoma survivors attending an out-patients clinic. Eur J Cancer Care 3(3):122-132, 1994.

81. Zittoun R: Quality of life in hematological malignancies with brief reference to bone marrow transplantation (editorial). Leuk Res 17(9):727-731, 1993.

82. Curbow B, Somerfield MR, Baker F, et al: Personal changes, dispositional optimism, and psychological adjustment to bone marrow transplant. J Behav Med 16:423-442, 1993.

83. Brody J: Children need special help when a parent has cancer. The New York Times Health, Wednesday, February 12, 1997.

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9. The Webster/Cella Article Reviewed

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Cancer treatment often has debilitating effects on the patients who receive it. Chemotherapy regimens can produce toxicities, such as gastrointestinal disturbances, hematologic deficiencies, fatigue, and neurotoxicity. Patients typically undergo these chemotherapy regimens to increase their disease-free survival time. Given that these therapies can negatively affect a patient's quality of life (QOL), treatments need to provide clear curative potential and/or survival benefits to offset detrimental effects on QOL.

Webster and Cella describe a case in which the benefits exchanged for the risks of therapy are unclear. As they describe, the therapies for low-grade non-Hodgkin's lymphoma (NHL) do not provide a clear benefit in terms of cure or overall survival. The authors therefore conclude that extensive treatment may not be warranted because of the great impact of these therapies on QOL.

When Are the QOL Consequences of Treatment Important?

We concur with Webster and Cella that QOL should be considered when making treatment decisions. There are several clear-cut circumstances in which the effects of treatment on QOL become an important decision-making tool. For example, the QOL consequences of treatment are particularly significant when the treatments being considered yield similar advantages in survival but have different toxicities.[1] This appears to be the case for the treatment options for low-grade NHL, as described by Webster and Cella.

Multiple treatment options exist, including observation only, that have little effect on overall survival but a highly variable impact on QOL. However, these treatments do appear to differ in how they affect other disease related variables, such as the speed of treatment response and time to recurrence.

Although overall survival is usually considered to be the "bottom line" in evaluating therapies, treatment efficacy in terms of time to recurrence should not be underemphasized. For a patient facing the long-term management of a chronic, incurable disease, the amount of time that he or she remains free of disease or with stable disease may be important. This is particularly true if the disease itself produces debilitating symptoms. However, for patients whose disease does not manifest serious symptoms, as is the case for many individuals with low-grade NHL, the advantage provided by a longer time to progression may be primarily psychological.

According to Webster and Cella, for patients with low-grade NHL, progression is slow, symptoms are few, and therapies offer little survival advantage. Thus, the complexity of QOL considerations must be carefully evaluated.

To date, research on the QOL of patients with low-grade NHL is limited. Even the data presented by Webster and Cella are not specific to low-grade NHL. Thus, more research is needed before strong conclusions can be made about treatment strategies for low-grade NHL that optimize both medical benefit and QOL.

Assessing Patients' Preferences

Although QOL may be compromised as the result of treatment, patients may be willing to endure these difficulties if therapy offers a longer symptom-free interval, or even the remote chance of cure or increased survival. The ambiguity surrounding the appropriateness of treatment for low-grade NHL indicates the need for information on patients' preferences for treatment outcomes, taking into account both changes in QOL and life expectancy.

One group of methods for quantifying patient's desires regarding treatment decisions is the assessment of utilities, or patient preferences. Utilities are used by decision scientists in evaluating treatment options based on a patient's preference for a particular health state.[2] A patient-generated utility is a measure of the patient's perception of the degree of impact of a particular outcome, such as neurologic problems or infertility. Utility is often assessed using such methods as the time trade-off, which seeks to determine the number of years of healthy life that a participant is willing to "trade off" for remaining free of an adverse health condition.

Utilities assess the value of a health state or outcome in reference to a universal standard, such as time, money, or risk of death.[3] This assessment technique is particularly useful when the same adverse event may be perceived differently by different people. These preferences can then be incorporated into formal decision-analytic models to determine the optimal treatment choice.

Need for Psychosocial Interventions

Even when treatment decisions take patient preferences into account, the management of the disease is likely to have consequences for patients' QOL. Patients who receive aggressive treatment must cope with the difficult side effects of chemotherapy. Patients who opt for the strategy of "watchful waiting" may experience stress and anxiety related to not treating the disease.

The impact of low-grade NHL on patients' QOL points to the need for psychosocial interventions to aid psychological adjustment and improve QOL. These programs may be implemented regardless of the treatment strategy chosen.

Several recent reviews have documented the effectiveness of psychosocial interventions in helping cancer patients adjust to their diagnosis and treatment.[4-7] Cognitive and behavioral interventions, such as guided imagery and progressive muscle relaxation, have been found to effectively reduce chemotherapy-induced symptoms and conditioned side effects, such as nausea and vomiting (see Fawzy et al[5]). In addition, cognitive-behavioral and more general support group-based interventions can be effective in improving psychological well-being and increasing overall survival time.[8,9] Group or

individual psychosocial intervention programs can be useful at different stages of disease and treatment, and they need to be made available to all patients.

Although no studies have tested the use of such interventions to help patients cope with the stress of not treating a disease, this could be a fruitful area of research for both low-grade NHL and other cancer sites characterized by slow progression (eg, prostate cancer).

Treatment Risks vs Benefits

Although inclusion of QOL outcomes should be considered when making treatment decisions for diseases such as low-grade NHL, patients' preferences for the trade-off between treatment risks and benefits should also be considered. However, because current methods for assessing utilities are complex and may be impractical in some settings,[3] further methodologic research is needed to improve assessment techniques.

Patients need to be well informed of the consequences of a particular treatment decision, but they also need to be aware of the beneficial effects treatments can have on the disease process. Active involvement in group, individual, and/or personalized psychosocial intervention programs can be a useful adjunct to traditional medical treatment.

Unfortunately, for many patients, these types of programs are not available or affordable. Future research needs to definitively determine the cost-efficacy of these intervention programs so that they can be made available to all patients battling life-threatening illnesses.

References

1. Nayfield SG, Ganz PA, Moinpour CM, et al: Report from a National Cancer Institute (USA) workshop on quality of life assessment in cancer clinical trials. Qual Life Res 1:203-210, 1992.

2. Cantor SB: Decision analysis: Theory and application to medicine. Prim Care 22:261-270, 1995.

3. Weeks J: Taking quality of life into account in health economic analyses. J Natl Cancer Inst Monogr 20:23-27, 1996.

4. Andersen BL: Psychological interventions for cancer patients to enhance the quality of life. J Consult Clin Psychol 60(4):552-568, 1992.

5. Fawzy IF, Fawzy NW, Arndt LA, et al: Critical review of psychosocial interventions in cancer care. Arch Gen Psychiatry 52:100-113, 1995.

6. Meyer TJ, Mark MM: Effects of psychosocial interventions with adult cancer patients: A meta-analysis of randomized experiments. Health Psychol 14(2):101-108, 1995.

7. Baum A, Herberman H, Cohen L: Managing stress and managing illness: Survival and quality of life in chronic disease. J Clin Psychol Med Set 2(4):309-333, 1995.

8. Fawzy FI, Fawzy NW, Hyun CS, et al: Malignant melanoma: Effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. Arch Gen Psychiatry 50:681-689, 1993.

9. Spiegel D, Bloom JR, Kraemer HC, et al: Effect of psychosocial treatment on survival of patients with metastatic breast cancer. Lancet 2:888-891, 1989.

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10. The Webster/Cella Article Reviewed

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The management of patients with the less aggressive subtypes of non-Hodgkin's lymphoma remains a clinical challenge. As pointed out by Webster and Cella, this challenge relates, at least in part, to the comparatively long median survival that can be achieved in such patients with a wide variety of treatment approaches. However, it is very important to realize that not all patients with the indolent varieties of non-Hodgkin's lymphoma are the same.

New Classification of Lymphomas

Work by the International Lymphoma Study Group has stimulated a new way of thinking about the classification of the non-Hodgkin's lymphomas.[1] Rather than focus on morphologically defined entities, the emphasis has shifted toward identifying more specific clinicopathologic entities—ie, real diseases. This new approach to classification takes into account biological (ie, genetic, immunologic, and so on) and clinical observations, in addition to cell size, shape, and growth pattern.

The new classification system will allow investigators to focus on specific illnesses for clinical studies. This work has led to the acceptance of a number of "new" lymphomas that previously were unrecognized. These newly recognized entities, such as mantle cell lymphoma, mucosa-associated lymphoid tissue (MALT) lymphomas, and anaplastic large cell lymphoma, make up approximately 20% of all non-Hodgkin's lymphomas (Table 1).[2]

Given this new, and I believe improved, approach to labeling lymphomas, the study of "low-grade" non-Hodgkin's lymphomas becomes inappropriate. Rather, studies should focus on small lymphocytic lymphoma, follicular lymphoma, MALT lymphoma, and other specific lymphomas. Each of these illnesses has a different natural history and response to available therapies, and lumping them together risks missing important information.

Quality of Life Issues

The report by Webster and Cella focuses on data generated from patients with follicular lymphoma. This diagnosis represents 20% to 25% of all non-Hodgkin's lymphomas diagnosed worldwide and more than 25% of those diagnosed in North America.[2] It is the best-studied indolent lymphoma and the disease to which most of their comments apply. However, follicular lymphoma is not a uniform disease, and all patients with this diagnosis should not be approached in the same way.

The development of the International Prognostic Index improved clinicians' ability to subcategorize patients with diffuse large cell lymphoma.[3] However, it has become apparent that this system of predicting survival of patients with lymphoma applies to the less aggressive lymphomas as well as the more aggressive subtypes.

Follicular lymphoma is thought to have a good outlook because most patients have favorable risk factors in the International Prognostic Index and a prolonged survival. However, a subset of these patients have a number of adverse risk factors and a survival as poor as any subgroup of patients with aggressive lymphoma.[2] Certainly, these latter patients will require a different management approach.

Quality of life has been a difficult issue to study in patients with cancers, as well as other diseases. However, I believe that some points are clear. One fact that has been surprising to many clinicians is that, when asked, patients seem to value increased survival over any other factor and are willing to accept surprising risks to achieve modest increases in survival. This leads back to the most frustrating question in the management of patients with follicular lymphoma: Does any therapy significantly modify the course of the illness?

Unfortunately, we have no completed, randomized trials to help answer this important question. In particular, no randomized trial comparing therapy to no therapy has been conducted. I doubt that any clinician who cares for patients with lymphoma questions the positive effect of treatment on their clinical course, although treatment can be withheld in many patients until symptoms develop. The debate centers on the timing of therapy and the relative merits of more vs less intensive approaches.

The management of indolent lymphomas, such as follicular lymphoma, is likely to remain a source of controversy for many years. Until definitive answers are available, this field remains one where the art of practicing medicine is still extremely important.

References

1. Harris NJ, Jaffe ES, Stein H, et al: A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 84:1361, 1994.

2. Evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 89:3909, 1997.

3. Project: A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 329:987, 1993.

Treatment of Patients With Low-Grade B-Cell Lymphoma With the Combination of Chimeric Anti-CD20 Monoclonal Antibody and CHOP Chemotherapy

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Purpose: To determine the safety and efficacy of the combination of the chimeric anti-CD20 antibody, Rituxan (Rituximab, IDEC-C2B8; IDEC Pharmaceuticals Corporation, San Diego, CA), and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy.

Patients and Methods: Forty patients with low-grade or follicular B-cell non-Hodgkin's lymphoma received six infusions of Rituxan (375 mg/m^2 per dose) in combination with six doses of CHOP chemotherapy.

Results: The overall response rate was 95% (38 of 40 patients). Twenty-two patients experienced a complete response (55%), 16 patients had a partial response (40%), and two patients, who received no treatment, were classified as nonresponders. Medians for duration of response and time to progression had not been reached after a median observation time of 29 + months. Twenty-eight of 38 assessable patients (74%) continued in remission during this median follow-up period. The most frequent adverse events attributable to CHOP were alopecia (38 patients), neutropenia (31 patients), and fever (23 patients). The most frequent events attributed to Rituxan were fever and chills, observed primarily with the first infusion. No quantifiable immune response to the chimeric antibody was detected. In a subset of 18 patients, the *bcl-2* [t(14;18)] translocation was positive in eight patients; seven of these patients had complete remissions and converted to polymerase chain reaction (PCR) negativity by completion of therapy.

Conclusion: This is the first report demonstrating the safety and efficacy of Rituxan anti-CD20 chimeric antibody in combination with standard-dose systemic chemotherapy in the treatment of indolent B-cell lymphoma. The clinical responses suggest an additive therapeutic benefit for the combination with no significant added toxicity. The conversion of *bcl-2* from positive to negative by PCR in blood and/or marrow suggests possible clearing of minimal residual disease not previously demonstrated by CHOP chemotherapy alone.

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THE NON-HODGKIN'S LYMPHOMAS (NHLs) are a diverse group of lymphoid neoplasms that collectively rank fifth in cancer incidence and mortality.[1,2] The prevalence of NHL has been increasing during the last two decades, and it is estimated that approximately 55,400 new cases and 24,900 deaths will occur in 1998.[2] Recognized since the 1950s as a distinct group of diseases, NHLs range from indolent malignancies (low-grade histologies) to rapidly growing and highly aggressive tumors (high-grade histologies). The overall median age at presentation is 42 years (58 years for low grade), and the incidence increases with advancing age.[3] The majority of NHLs are of B-cell origin,[4] with more than 90% of patients expressing the CD20 antigen.[5]

In general, low-grade or follicular NHL is assumed to have an indolent course when compared with intermediate- and high-grade NHL. Although treatment of low-grade follicular lymphomas with standard chemotherapeutic regimens is characteristically associated with a high initial response rate, the clinical course consists of a pattern of repeated relapse. Subsequent remissions occur, but at a progressively lower rate and with a shorter duration.[6] Patients eventually succumb to the disease or its complications with a median survival of approximately 6.2 years.[7,8] For these reasons, novel therapeutic agents and strategies need to be evaluated in this group of patients.

Molecular research has identified the *bcl*-2 proto-oncogene as being associated with a t(14;18) chromosomal translocation, which has been reported to occur in approximately 50% of NHLs (80% low grade; 30% intermediate grade).[3] This chromosomal translocation moves the *bcl*-2 gene from chromosome 18 to the immunoglobulin heavy-chain locus on chromosome 14 and results in *bcl-2* activation. Resultant overexpression of *bcl-2* protein localizes to the mitochondrial membrane, nuclear membrane, endoplasmic reticulum, and cell membrane.[9] This results in inhibition

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of apoptosis (programmed cell death) and gives cells a survival advantage. B cells containing t(14;18) chromosomal translocation are believed to play a role in lymphomagenesis, possibly serving as the "first hit" in a "multi-hit" theory of carcinogenesis. By use of a sensitive, nested polymerase chain reaction (PCR) assay, cells containing the t(14;18) chromosomal translocation are detectable at an assay sensitivity of one *bcl-2*–positive cell in 10^5 to 10^6 normal cells.[10] In patients with documented B-cell lymphoma, serial analyses of *bcl-2* in blood and marrow by PCR could serve as a method for monitoring minimal residual disease.

Attempts to treat B-cell malignancies with monoclonal antibodies (mAbs) began more than a decade ago with monoclonal antibodies reactive with B-cell antigen idiotypes.[11,12] Customized anti-idiotypic monoclonal antibodies were developed and used alone or in combination with interferon alfa or chlorambucil. Significant clinical activity was observed; however, this type of murine monoclonal antibody therapy was limited by the development of human anti-mouse antibody responses, the relative inability of mouse antibodies to induce human immune effector mechanisms, and the occurrence of idiotype-negative relapses. The technology to alter antibodies genetically by joining the variable region genes of murine antibodies to human immunoglobulin constant region genes allowed the development of a mouse/human chimeric antibody with the demonstrated advantages of reduced immunogenicity and an enhanced ability to interact with human effector cells.

Rituxan (IDEC Pharmaceuticals Corporation, San Diego, CA) is a chimeric monoclonal anti-CD20 antibody that can deplete malignant B cells through complement-dependent cell cytotoxicity, antibody-dependent cell-mediated cytotoxicity,[13] and apoptotic mechanisms. It has also been shown to sensitize drug-resistant lymphoma cell lines to killing by cytotoxic drugs.[14] The monoclonal antibody has shown single agent activity in patients with low-grade or follicular lymphomas. Two previous phase I/II single agent, dose-escalation studies of Rituxan have been conducted in patients with relapsed or recurrent NHL. Fifteen patients were enrolled onto a single dose study (10 to 500 mg/m^2 of Rituxan), and 47 patients were enrolled onto a multiple dose study (125, 250, or 375 mg/m^2 weekly for 4 weeks). Clinical activity was noted in seven of 15 patients in the single dose trial, with two partial responses lasting 8.1 and 8.5 months and five minor responses.[15] In the phase II portion of the multiple dose (375 mg/m^2) Rituxan study, three complete responses and 14 partial responses were noted in 34 assessable patients, with a median response duration of 8.6 months.[16] Median time to progression (TTP) in these responders was 10.2 months; TTP exceeded 20 months in five patients and 30+ months in two patients. Adverse experiences were mostly grade 1 or 2 and consisted primarily of infusion-related events (fever, asthenia, chills, and, less commonly, bronchospasm, hypotension, and angioedema). Hematologic toxicity was usually mild and reversible.

Because of these encouraging results, a phase II open-label, single arm, multicenter study was designed to evaluate the safety and clinical activity of this new monoclonal antibody in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy in the treatment of patients with low-grade B-cell lymphoma. CHOP chemotherapy was chosen because this cytotoxic regimen is an effective first-line therapy for low-grade or follicular NHL. The rationale for the combination of Rituxan and CHOP includes single agent efficacy, non–cross-resistant mechanisms of action, non-overlapping toxicities, and in vitro synergy with certain cytotoxic drugs, including doxorubicin.

PATIENTS AND METHODS

Eligibility

The patient population in this study consisted of newly diagnosed and relapsed/refractory patients at least 18 years of age with histologically documented low-grade or follicular B-cell NHL and measurable progressive disease. Tumors were required to be CD20 positive. Patients were to have an expected survival of 3 months or more; a prestudy performance status of 0, 1, or 2 according to the World Health Organization scale; recovery from any significant toxicity associated with anticancer therapy; and adequate hematologic, renal, and hepatic function within 7 days of initial therapy. The following exclusion criteria applied: "bulky" disease (defined as any single mass > 10 cm in its greatest diameter); prior therapy with anthracyclines, anthrapyrazoles, or drugs that were classified at the time as investigational phase I or II antineoplastic agents; prior radioimmunotherapy; cancer radiotherapy, immunotherapy, or chemotherapy within 3 weeks of the scheduled first study treatment; nitrosourea or mitomycin therapy within 6 weeks of the first scheduled study therapy; or presence of CNS lymphoma. Other exclusion criteria were as follows: significantly impaired organ function, as measured by a serum creatinine level greater than 2.0 mg/dL, a total bilirubin level greater than 2.0 mg/dL, or an AST or alkaline phosphatase level more than 2 times normal; serious nonmalignant disease; active opportunistic infection; major surgery within 4 weeks; and previous or concomitant malignancy other than basal cell or squamous cell carcinoma of the skin, carcinoma-in-situ of the cervix, or other malignancy for which the patient had not been disease-free for at least 5 years. Patients with a New York Heart Association class III or IV heart disease or myocardial infarction within the past 6 months and patients with a left ventricular ejection fraction of less than 45% within 1 month of study enrollment were disqualified from entering onto the study. Patients who had prior anti-CD20 therapy were excluded, except for patients who were previously enrolled onto a clinical trial of Rituxan with negative human anti–chimeric antibody (HACA) serum titers. Patients with a nondemonstrable CD20-positive neoplastic B-cell population in lymph nodes or bone marrow were not included. Pregnant or lactating women and patients of childbearing

potential, unless using accepted birth control methods, were not allowed to enroll. Eligible patients signed a detailed written informed consent statement meeting the requirements of the institutional review board of the participating institution. Institutional review board approval was given for this study at each participating center.

PCR Assay for t(14;18)

The assay for the detection of cells with the t(14;18) chromosomal translocation by PCR uses a nested primer amplification specifically for either the major breakpoint region or the minor cluster region and was developed at Roswell Park Cancer Institute in collaboration with Dr. John Gribben. The PCR technique used in this study was essentially the same, with minor modifications, as that used and described by Gribben et al.[10] The assay will detect one in 10^5 to one in 10^6 t(14;18)-containing cells for either breakpoint region among a normal background and will discriminate all t(14;18) translocations that occur within these regions. Major breakpoint region- and minor cluster region-positive and -negative cell lines were used as controls. A separate PCR reaction was performed to amplify a region within the *bcl*-2 gene to act as an internal DNA quality control.

Treatment Design

This study consisted of a single treatment group. Patients were to receive a total of six intravenous infusions of 375 mg/m^2 of Rituxan and six cycles of CHOP, given every 3 weeks (Fig 1). Each CHOP cycle consisted of cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 (maximum dose, 2.0 mg), given intravenously on day 1, and oral prednisone 100 mg/m^2 on days 1 through 5. Rituxan was produced and supplied as a 5-mg/mL saline solution of antibody in 10-mL glass syringes. The mAb was further diluted in normal saline to a final concentration of 1 mg/mL and administered intravenously through a low-protein-binding 0.22-μm in-line filter. Rituxan infusions 1 and 2 were administered on days 1 and 6 before the first CHOP cycle, which started on day 8. Rituxan infusions 3 and 4 were given 2 days before the third and fifth CHOP cycles, respectively, and infusions 5 and 6 were given on days 134 and 141, respectively, after the sixth CHOP cycle. This mAb schedule was chosen to take advantage of three different characteristics of Rituxan in addition to its known clinical activity in NHL: (1) in vitro data demonstrating its ability to sensitize chemoresistant cell lines; therefore, doses 1 and 2 could be viewed as a form of induction immunotherapy that could possibly render chemoresistant cells chemosensitive; (2) in vitro data demonstrating that possible synergy with cytotoxic agents would best be effected by interim doses 3 and 4; and (3) the generally well-accepted belief that monoclonal antibodies are extremely effective in a minimal residual disease setting; thus, doses 5 and 6 could be viewed as being used as a "mop up" of residual lymphoma after completion of systemic chemotherapy.

If toxicity occurred during the mAb infusion, the infusion was to be slowed or temporarily discontinued and the patients were to be medicated as necessary with acetaminophen (for fever) or diphenhydramine (for rash, mucosal congestion, or other infusion-related reactions) and other medications as needed. Once the adverse events abated, the antibody infusion could be resumed at 50% of the previous rate and then escalated as tolerated. CHOP was to be administered according to the standard preparation and infusion procedures for each institution. If grade 3 neurotoxicity occurred at any time during the treatment period, vincristine could be discontinued at the investigator's discretion. Cyclophosphamide dose modification for hematologic toxicities was to be carried out according to an algorithm provided in the protocol. A patient whose treatment was interrupted for more than 3 weeks for either hematologic or nonhematologic toxicity was to be removed from the study. As stated in the informed consent, patients were allowed to withdraw from the study at any time. Furthermore, treatment was discontinued if disease progression was noted or if, in the opinion of the investigator, it was not in the patient's best interest to continue.

Oral premedication with 650 mg of acetaminophen and 50 to 100 mg of diphenhydramine hydrochloride could be administered 30 to 60 minutes before each mAb infusion. No concurrent antineoplastic therapy was allowed except for localized brain radiotherapy for CNS lymphoma. Surgery that did not affect any sentinel lesions was allowed, and surgery on sentinel lesions was allowed only to detect mAb tumor penetration.

Evaluation

All patients were assessable for the intent-to-treat analysis of tumor response and toxicity. The primary efficacy measure was the response of B-cell lymphoma to treatment as determined by the investigator and confirmed by the sponsor. Lesion evaluations occurred at baseline, before the third cycle of CHOP, after the completion of therapy, and every 4 months thereafter until disease progression (PD) was observed. Any evaluation indicating the onset of a partial response (PR) or complete response (CR) (Table 1) was followed by a confirmatory evaluation no sooner than 28 days later. Ninety-five percent confidence intervals for the response rates were calculated.

Secondary efficacy variables were the TTP and the response duration (PD-free interval). The TTP was measured from the date of the first Rituxan infusion to the date of PD or the date of last contact, whichever was earlier. Response duration was measured from the date of the first

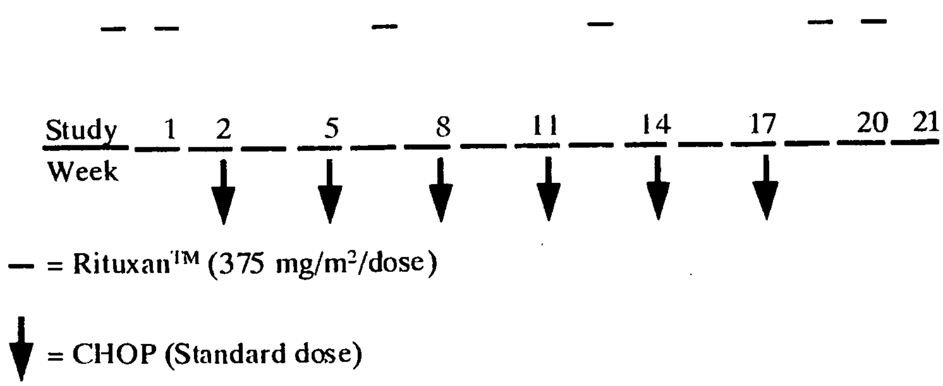

Fig 1. Treatment schedule. Patients received a total of six intravenous infusions of 375 mg/m^2 of Rituxan and six cycles of CHOP given every 3 weeks.

Table 1. Response Criteria for NHL

Complete response
- No evidence of disease or areas of residual abnormality > 1.0 cm^2 converting from gallium positivity to gallium negativity or proven to be secondary to residual fibrosis by biopsy
- No new lesions
- Confirmed at ≥ 28 days
- Asymptomatic
- No decrease in performance status
- Bone marrow negative (if initially positive)

Partial response
- SPD decrease from baseline ≥ 50%
- No new lesions
- Confirmed at ≥ 28 days

Stable disease
- < 50% decrease in SPD from baseline
- < 50% increase from baseline or nadir
- No new lesions

Progressive disease
- SPD increased ≥ 50% from nadir
- New lesions

Abbreviation: SPD, sum of the products of the perpendicular diameters.

observation of response to the date of PD or the date of last contact, whichever was earlier.

Patients were monitored for the development of an HACA response (samples assayed at the Clinical Immunology Laboratory, IDEC Pharmaceuticals Corporation). Quantitative immunoglobulin levels were also measured at the individual treatment sites.

Each patient's NHL was classified histologically at baseline using International Working Formulation (IWF) criteria, and the stage of each patient's disease was assigned according to the Ann Arbor classification.

Pretreatment *bcl-2* [t(14;18)] analysis by PCR was performed in the Laboratory of Molecular Diagnostics at Roswell Park Cancer Institute on peripheral blood and separately pooled bilateral bone marrow aspirate and biopsy samples from 18 patients enrolled onto the study at Roswell Park Cancer Institute. Serial samples for PCR analysis were obtained in those patients testing *bcl-2* positive at baseline.

RESULTS

Patient Demographics and Disposition

The clinical features of the 40 patients (31 previously untreated) enrolled onto this study are listed in Table 2. Thirty-five of the 40 patients received all six infusions of Rituxan and six cycles of CHOP. Two patients were withdrawn from the study before treatment initiation (one patient withdrew for personal reasons, and one patient was withdrawn by the treating physician because of the discovery of lymphomatous involvement of the central nervous system). Three patients discontinued study treatment early (one patient withdrew for personal reasons, one patient withdrew owing to the development of an epidural abscess, and one patient died from reactivation of hepatitis B infection). All 40 patients are included in the intent-to-treat analysis.

Treatment Dose-Intensity

The Rituxan dose was not modified in the 38 patients who received treatment. Doses of one or more chemotherapy agents of the CHOP regimen were adjusted in only 13 patients at some time during the course of the study. In addition, the administration of at least one cycle of CHOP was delayed in six patients by 1 to 3 weeks. Dose-intensity was calculated for cyclophosphamide, doxorubicin, vincristine, and prednisone in each patient as the actual dose received in milligrams per meters squared per week, divided by the calculated total dose in milligrams per meters squared per week. This analysis revealed an average dose-intensity of 0.95 for cyclosphophamide, 0.97 for doxorubicin, 0.95 for vincristine, and 0.95 for prednisone. The average dose-intensity for all of the agents in the CHOP regimen was 0.96 in this chemoimmunotherapy study.

Table 2. Patient Demographics

Characteristic	No.	%
Age, years		
Median	48.5	
Range	29-77	
Sex, male/female	21/19	52.5/47.5
Performance status*		
0	31	78
1	7	18
2	2	5
Time from diagnosis,† years		
Median	0.21	
Range	0.02-8.29	
Histologic grade‡		
A	9	23
B	17	43
C	13	33
D	1	3
Stage§		
I/II	5	13
III	11	28
IV	24	60
Prior lymphoma treatment		
No	31	78
Yes	9	22
Extranodal disease		
No	11	28
Yes	29	72
Elevated serum LDH		
No	29	72
Yes	11	28
Bone marrow involvement		
No	18	45
Yes	22	55

Abbreviation: LDH, lactate dehydrogenase.
*World Health Organization classification.
†Years from diagnosis date to first Rituxan infusion.
‡IWF classification.
§Stage at initial diagnosis.

Response to Therapy

Median time to response was 47 days (range, 15 to 236 days). The overall response rate to the combination of CHOP and Rituxan treatment was 95% (95% confidence interval, 88% to 100%) in the intent-to-treat patient population (Table 3). Twenty-two patients (55%) experienced a CR, and 16 patients (40%) had a PR. Thus, only the two patients who were withdrawn from the study before the initiation of trial therapy were classified as nonresponders (one with an IWF histologic classification of A and the other, B). Response rates were also evaluated for patient subpopulations, including those with extranodal disease, an elevated serum lactate dehydrogenase concentration, bone marrow involvement, an age of 60 years or more, or bulky disease (Table 3). Combination Rituxan and CHOP therapy achieved at least a partial response in all of the patients, and the complete response rate was less than 45% only for those patients with bulky disease. Twenty-eight (74%) of 38 assessable patients continued in remission after a median observation time of 29 months (Fig 2).

There were 24 assessable (plus one unassessable) newly diagnosed patients with follicular histology, and they all responded to therapy (16 CR and eight PR). The median duration of response was yet to be reached at 27.8+ months. There was no significant difference in duration of response between naive and previously treated patients. There were nine patients with IWF type A histology. Of these, one patient was unassessable, and the other eight patients were responders (three CR and five PR). The median duration of response for the IWF type A patients had not been yet reached at 17+ months. Five of the eight patients were in ongoing remissions. At that time, there was no significant difference in rate or duration of response when these patients were compared with the rest of the study patients.

Eight of the nine patients who had received chemotherapy treatments before study entry responded to therapy with Rituxan and CHOP (Table 4). Five of these responses were complete; two of the complete responses occurred in patients who had experienced either progressive disease or a partial response with their last prior chemotherapy regimen (cyclophosphamide, vincristine, prednisone and chlorambucil, prednisone, respectively).

Table 3. Response to Therapy

		Response					
		CR		PR		CR + PR	
Patient Group	No.	No.	%	No.	%	No.	%
Intent-to-treat	40	22	55	16	40	38	95
Extranodal disease	29	15	52	14	48	29	100
Elevated LDH	11	5	45	6	55	11	100
Bone marrow involvement	22	11	50	11	50	22	100
Age ≥ 60 years	11	5	45	6	55	11	100
Bulky disease*	14	4	29	10	71	14	100

Abbreviation: LDH, lactate dehydrogenase.

*Patients who had a lesion measuring at least 5 cm (but no more than 10 cm) in the largest diameter.

Safety

The most frequently experienced adverse events in this trial were neutropenia (31 patients), alopecia (30 patients), nausea (27 patients), and fever (23 patients). Adverse events that occurred in more than 10% of patients and grade 3 or 4 events are listed in descending order in Table 5. Eight patients were hospitalized with febrile neutropenia and two patients with neutropenia and a documented infection. Most (75%) of the adverse events were attributed to CHOP chemotherapy by the treating physicians. The one death that occurred on study was secondary to reactivation of hepatitis B with resultant hepatic failure and hepatorenal syndrome. Rapid deterioration of liver function tests followed the fifth cycle of CHOP chemotherapy. The most frequent events attributed to mAb treatments were infusion-related events. These events (19% overall) were all grade 1 or 2 in severity and included fever (12 patients), chills (nine patients), and pruritus (six patients). The infusion-related events occurred most frequently with the initial Rituxan infusion and decreased in frequency with subsequent infusions.

A quantifiable immune response to the chimeric antibody HACA was not detected in any patient (limit of detection, 0.57 μg/mL). The mean serum immunoglobulin (Ig) levels for IgG, IgA, and IgM remained within the normal range throughout the trial. Immunoglobulin levels decreased by 50% from baseline and fell below the normal range in 13 patients. Two patients experienced a drop in IgG levels of more than 50% from baseline at days 88 and 146; one (patient no. 27) recovered to normal levels or to within 20% of baseline at day 175. Four patients reported greater than 50% drop from baseline in IgA at days 162, 51, 169, and 97; two recovered to normal levels or to within 20% of baseline at days 92 and 98. Seven patients experienced a drop in IgM levels of more than 50% below baseline; two patients recovered to normal values or to within 20% of baseline at day 176. The immunoglobulin levels for the remaining nine patients had not recovered by the time of the last follow-up examination.

DISCUSSION

Treatment choices for advanced stage low-grade or follicular NHL (IWF type A, B, C, D) have included radiotherapy, single agent chemotherapy, combination chemotherapy, immunotherapy, and combined modalities. Early studies of combination chemotherapy regimens containing anthracyclines resulted in complete response rates of 30% to 40% but

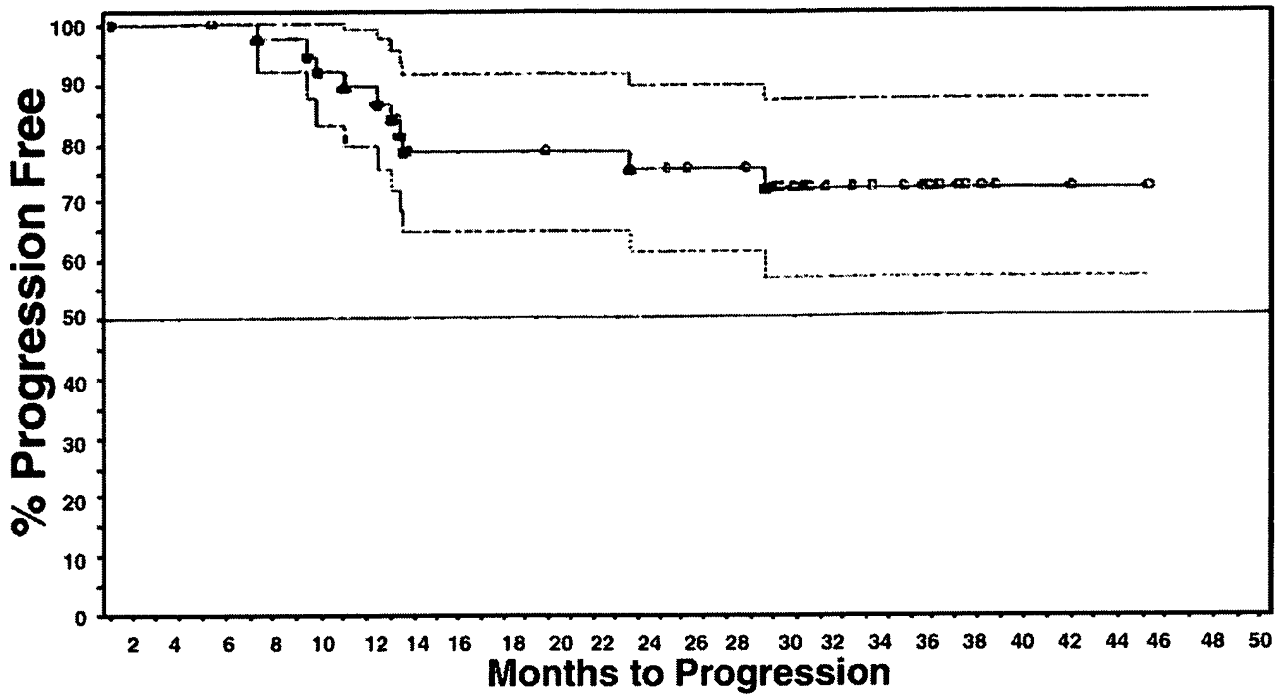

Fig 2. Kaplan-Meier analysis of time to progression, performed in 38 assessable patients.

with no difference in survival as compared with other treatment modalities.[17] The CHOP chemotherapy regimen has been studied extensively in NHL, and high response rates have been reported.[18-24] In 1976, the Southwest Oncology Group[18] (SWOG) reported on 204 stage III and IV assessable patients treated with CHOP chemotherapy that was repeated every 2 to 3 weeks (for six or more cycles), followed by maintenance with cyclophosphamide, vincristine, prednisone or vincristine, cytarabine, prednisone every 3 to 4 weeks for a total of 18 months in patients achieving CR status. A 78% complete response rate was reported in the subpopulation of 73 patients with nodular lymphoma and a 61% response rate in the subpopulation of 23 patients with well-differentiated lymphocytic lymphoma.

Jones et al[19] reviewed the SWOG experience with CHOP from 1997 to 1983 in patients with no prior chemotherapy, advanced stage (III or IV), or recurrence after chemotherapy (any stage). Treatment was administered every 3 weeks for eight cycles. In 281 patients with favorable histology, the CR rate was 57% to 64%, without significant differences between CHOP or CHOP plus levamisole with or without BCG vaccine. Subsequently, Dana et al[20] reviewed these two SWOG studies, as well as an additional SWOG lymphoma study, and identified 415 stage III or IV low-grade lymphoma patients who had no prior therapy and were treated with full-dose CHOP. A CR rate of 64% and a median survival duration of 6.9 years was observed in these patients. Overall, chemotherapy or levamisole-BCG maintenance treatment did not increase the overall survival of patients achieving a CR with CHOP.

McLaughlin et al[22] added bleomycin and radiotherapy to the CHOP regimen for treatment of 74 patients with stage III follicular lymphoma. Chemotherapy was administered every 3 weeks for 10 cycles, with radiotherapy given after two cycles of chemotherapy. All patients were previously untreated. These investigators reported a 97% CR rate for

Table 4. Tumor Response and Duration in Nine Previously Treated Patients: Last Chemotherapy Versus CHOP + Rituxan

Patient No.	Last Prior Chemotherapy: Response	Last Prior Chemotherapy: Response Duration* (months)	CHOP + Rituxan: Response	CHOP + Rituxan: Response Duration* (months)
2	PR	4	PR	5.1
6	CR	5	CR	10.2
13	PR	28	CR	35.7+
17	PD	0	CR	33.3+
19	CR	15	PR	4.1
22	CR	24	PR	10.5+
27	CR	12	CR	26.3+
28	CR	50	CR	28.5+
29†	—	—	—	—

*Median observation time, 29+ months.

†Patient withdrew from study before initiation of CHOP + Rituxan treatment, and prior response data were not available.

Table 5. All Adverse Events by Grade (Incidence by Patient*) (N = 40)

	Grade				Total	
	1	2	3	4	No.	%
Any adverse event	1	7	12	18	38	95.0
Neutropenia	2	5	9	15	31	77.5
Alopecia	7	16	6	1	30	75.0
Nausea	20	6	1	0	27	67.5
Fever	5	16	2	0	23	57.5
Leukopenia	5	4	6	4	19	47.5
Anemia	0	14	2	0	16	40.0
Asthenia	12	3	1	0	16	40.0
Vomiting	6	8	1	0	15	37.5
Infection	8	5	1	0	14	35.5
Headache	8	5	0	0	13	32.5
Anxiety	8	3	0	0	11	27.5
Chills	6	4	1	0	11	27.5
Constipation	7	4	0	0	11	27.5
Pain	7	3	0	0	10	25.0
Pharyngitis	9	1	0	0	10	25.0
Rhinitis	9	1	0	0	10	25.0
Cough increase	7	2	0	0	9	22.0
Dyspepsia	6	3	0	0	9	22.0
Myalgia	6	3	0	0	9	22.0
Stomatitis	3	5	1	0	9	22.0
Arthralgia	6	1	1	0	8	20.0
Dyspnea	4	3	1	0	8	20.0
Insomnia	7	1	0	0	8	20.0
Thrombocytopenia	3	1	2	2	8	20.0
Diarrhea	5	1	0	0	6	15.0
Esophagitis	3	2	1	0	6	15.0
Pruritus	5	1	0	0	6	15.0
Sinusitis	4	2	0	0	6	15.0
Dizziness	4	1	0	0	5	12.5
Hyperglycemia	1	2	1	1	5	12.5
Hypertonia	4	1	0	0	5	12.5
Abdominal pain	4	0	1	0	5	12.5
Paresthesia	5	0	0	0	5	12.5
Weight decrease	3	2	0	0	5	12.5

*At least 5% of patients and any grade 3 or 4 event.

follicular small-cleaved NHL, a 73% CR rate for follicular-mixed NHL, and a 57% CR rate for patients with follicular large-cell NHL. The overall survival rate was 71% at 5 years and 56% at 7 years; 5-year relapse-free survival was 52%. Survival was influenced by histology, with follicular small-cleaved cell (n = 38) and follicular-mixed (n = 15) (91% and 84% survival at 5 years, respectively) more successful than follicular large-cell (n = 21) (40% survival at 5 years).

It should be noted that many of these early published CHOP response data were determined at a time when computed tomographic scanning was not available and/or a variety of restaging studies were performed that were less stringent than the ones used in the current trial. In a more recent study,[25] in which 83 patients with previously untreated follicular lymphoma (IWF types B and C) received six to eight cycles of CHOP chemotherapy, staging studies included computed tomographic scans, flow cytometric analysis of peripheral blood and bone marrow samples in every patient, and gallium scanning as needed to determine the extent of disease. In contrast to the high response rates reported in earlier studies, only 28 patients (36%; 90% confidence interval, 27% to 46%) achieved a CR[25] with more stringent clinical staging evaluations. The 55% CR rate in the 40 intent-to-treat patients (including nine patients with prior chemotherapy) on our current study compares favorably with this more recent CHOP study and strongly suggests that Rituxan contributes additional antitumor activity to patients treated with six cycles of CHOP chemotherapy, as evaluated by similar staging studies.

The toxicity of CHOP chemotherapy has been described in studies of low-, intermediate-, and high-grade lymphoma. In a randomized study comparing CHOP with other aggressive regimens, 1% of patients experienced fatal toxicity in the CHOP group and an additional 31% developed grade 4 life-threatening toxicities.[26] SWOG[19] reported fatal toxicities in 3% of patients and grade 3 and 4 toxicities in an additional 28% of patients. Hematologic toxicity with secondary infection and anemia were the most prominent adverse effects. In one study, six of 20 patients (30%) developed pancytopenia (absolute granulocyte count < 500/mm^3 and platelets < 50,000/mm^3). The Eastern Cooperative Oncology Group (ECOG) reported that 17 of 19 patients (89%) developed grade 3 and 4 leukopenia, two of 19 patients (11%) had grade 3 thrombocytopenia, and 14 of 19 patients (74%) had grade 3 anemia. Sixty-three percent of patients who received CHOP required at least one admission to the hospital. Most hospitalizations were due to neutropenic fevers (nine of 19 patients [47%] had a total of 13 admissions).[27] In another study, six of 20 patients developed documented infections.[28] Furthermore, reactivation of hepatitis B has been attributed to immunosuppression secondary to cytotoxic drugs, corticosteroids, etc, in other studies.[29-31] Grade 1 neurologic disorders[32] developed in 59% of patients in one study, and ECOG reported that two (11%) of 19 patients had developed grade 3 neurologic adverse events related to vincristine. Sixty percent of patients developed grade 1 and another 30% developed grade 2 gastrointestinal toxicity. One hundred percent of patients developed alopecia. Forty percent of patients developed a decrease in left ventricular ejection fraction, and 20% experienced cardiac arrhythmias. One of 20 patients developed congestive heart failure after a cumulative doxorubicin dose of 294 mg/m^2. CHOP has also been associated with anxiety, rash, and decreased sexual interest.[33]

In the present study of 31 patients with untreated NHL and nine patients with relapsed low-grade or follicular NHL, the combination of Rituxan and CHOP chemotherapy yielded an overall response rate of 95% (38 of 40 patients) in the intent-to-treat population, with a median time to progression

that had not yet been reached at a median observation time of 29+ months. Patients with poor prognostic factors, such as extranodal disease, elevated serum lactate dehydrogenase levels, bone marrow involvement, advanced age, and bulky disease, responded to the combination of Rituxan and CHOP.

The *bcl*-2 proto-oncogene is associated with a t(14;18) chromosomal translocation and has been reported in approximately 80% of low-grade NHL and 30% of intermediate-grade NHL.[3] The resultant *bcl-2* activation leads to overexpression of *bcl-2* protein, which inhibits apoptosis and is believed to play an important role in lymphomagenesis. Gribben et al[10,34] have previously demonstrated that the presence of *bcl-2* translocation-positive cells in marrow after autologous bone marrow transplantation, as measured by a sensitive PCR assay, has prognostic value in predicting relapse. In the CHOP-Rituxan study, serial *bcl-2* analysis was not planned by protocol but was evaluated prospectively at one center (Roswell Park Cancer Institute) using essentially the same PCR assay as that used by Gribben et al. Eight of 18 tested patients were found to be *bcl-2* positive in blood and/or marrow pretreatment. Seven of eight patients converted to PCR negativity after the completion of therapy. Six of these patients underwent elective autologous bone marrow collection posttreatment, with pooled buffy coat specimens confirming PCR negativity in all six patients. Unpurged stem cells were cryopreserved and are available for future autologous bone marrow transplantation if needed in those patients requiring dose-intensive therapy of refractory disease. The seven patients becoming *bcl-2* negative also had documented complete remissions by standard restaging evaluations and were considered to have achieved molecular complete remissions. Six patients remained in CR, and five of seven patients remained PCR negative by serial analysis for at least 24 months or longer. Standard-dose CHOP alone is incapable of converting *bcl-2*–positive bone marrow to PCR negativity.[35] The potential impact of achieving and maintaining a posttreatment molecular CR with respect to disease-free and overall survival in *bcl-2*–positive NHL patients in a non–autologous bone marrow transplantation setting will be studied prospectively in large cohorts of patients in future Rituxan trials.

These clinical findings suggest that Rituxan adds therapeutic benefit to CHOP therapy without causing significant additional toxicity. Owing to the promising results from this chemoimmunotherapy trial, a multicenter study of this combination in previously untreated intermediate- and high-grade NHL patients has recently been completed and a single institution study in previously untreated mantle-cell lymphoma patients is ongoing at Dana-Farber Cancer Institute. Many other clinical trials for the study of Rituxan in combination with a variety of other cytotoxic agents for the treatment of CD20-positive neoplasms in a variety of clinical settings are being planned for the future.

REFERENCES

1. Parker S, Tong T, Bolden S, et al: Cancer statistics, 1996. CA Cancer J Clin 46:5-27, 1996

2. Landis S, Murray T, Bolden S, et al: Cancer statistics, 1998. CA Cancer J Clin 48:6-29, 1998

3. Longo D, DeVita V, Jaffe E, et al: Lymphocytic lymphomas, in DeVita VT Jr, Hellman S, Rosenberg S (eds): Cancer: Principles & Practice of Oncology (ed 4). Philadelphia, PA, Lippincott, 1993, pp 1859-1927

4. Harris N, Jaffe E, Stein H, et al: Lymphoma classification proposal: Clarification. Blood 85:857-860, 1995

5. Anderson K, Bates M, Slaughenhoupt B, et al: Expression of human B cell-associated antigens on leukemias and lymphomas: A model of human B cell differentiation. Blood 63:1424-1433, 1984

6. Aisenberg A: Coherent view of non-Hodgkin's lymphoma. J Clin Oncol 13:2656-75, 1995

7. Rosenberg S, Berard C, Brown J, et al: National Cancer Institute sponsored study of classification of non-Hodgkin's lymphomas: Summary and description of a working formulation for clinical usage: The Non-Hodgkin's Lymphoma Pathologic Classification Project. Cancer 49:2112-2135, 1982

8. Lukes R, Collins R: Immunologic characterization of human malignant lymphomas. Cancer 34:1488, 1974

9. Krajewski S, Tanaka S, Takayama S, et al: Investigation of the subcellular distribution of the *bcl-2* oncoprotein: Residence in the nuclear envelope, endoplasmic reticulum, and outer mitochondrial membranes. Cancer Res 53:4701-4714, 1993

10. Gribben J, Neuberg D, Freedman A, et al: Detection by polymerase chain reaction of residual cells with the *bcl-2* translocation is associated with increased risk of relapse after autologous bone marrow transplantation for B-cell lymphoma. Blood 81:3449-3457, 1993

11. Maloney D, Levy R, Miller R: Monoclonal anti-idiotype therapy of B-cell lymphoma. Biol Ther Cancer 2:1-10, 1992

12. Maloney D, Brown S, Czerwinski D, et al: Monoclonal anti-idiotype antibody therapy of B-cell lymphoma: The addition of a short course of chemotherapy does not interfere with the antitumor effect nor prevent the emergence of idiotype-negative variant cells. Blood 80:1502-1510, 1992

13. Reff M, Carner K, Chambers K, et al: Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 83:435-445, 1994

14. Demidem A, Lam T, Alas S, et al: Chimeric anti-CD20 (IDEC-C2B8) monoclonal antibody sensitizes a B cell lymphoma cell line to cell killing by cytotoxic drugs. Cancer Biother Radiopharm 12:177-186, 1997

15. Maloney D, Liles T, Czerwinski D, et al: Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. Blood 84:2457-2466, 1994

16. Maloney D, Grillo-López A, White C, et al: IDEC-C2B8 (RituxanAB) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood 90:2188-2195, 1997

17. Cabanillas F, Rodriguez V, Freireich E: Improvement in complete response rate, duration of response and survival with adriamycin combination chemotherapy for non-Hodgkin's lymphoma: A prognostic

factor comparison of two regimens. Med Pediatr Oncol 4:321-331, 1978

18. McKelvey E, Gottlieb J, Wilson H, et al: Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. Cancer 38:1484-1493, 1976

19. Jones S, Grozea P, Miller T, et al: Chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone alone or with levamisole or with levamisole plus BCG for malignant lymphoma: A Southwest Oncology Group Study. J Clin Oncol 3:1318-1324, 1985

20. Dana B, Dahlberg S, Nathwani B, et al: Long-term follow-up of patients with low-grade malignant lymphomas treated with doxorubicin-based chemotherapy or chemoimmunotherapy. J Clin Oncol 11:644-651, 1993

21. Rodriguez V, Cabanillas F, Burgess M, et al: Combination chemotherapy ("CHOP-Bleo") in advanced (non-Hodgkin's) malignant lymphoma. Blood 49:325-333, 1977

22. McLaughlin P, Fuller L, Velasquez W, et al: Stage III follicular lymphoma: Durable remissions with a combined chemotherapy-radiotherapy regimen. J Clin Oncol 5:867-874, 1987

23. Sullivan K, Neiman P, Kadin M, et al: Combined modality therapy of advanced non-Hodgkin's lymphoma: An analysis of remission duration and survival in 95 patients. Blood 62:51-61, 1983

24. Rijlaarsdam J, Toonstra J, Meijer O, et al: Treatment of primary cutaneous B-cell lymphomas of follicle center cell origin: A clinical follow-up study of 55 patients treated with radiotherapy or polychemotherapy. J Clin Oncol 14:549-555, 1996

25. Freedman A, Gribben J, Neuberg D, et al: High-dose therapy and autologous bone marrow transplantation in patients with follicular lymphoma during first remission. Blood 88:2780-2786, 1996

26. Fisher R, Gaynor E, Dahlberg S, et al: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 328:1002-1006, 1993

27. Meyer R, Browman G, Samosh M, et al: Randomized phase II comparison of standard CHOP with weekly CHOP in elderly patients with non-Hodgkin's lymphoma. J Clin Oncol 13:2386-2393, 1995

28. Brusamolino E, Bertini M, Guidi S, et al: CHOP versus CNOP (N = mitoxantrone) in non-Hodgkin's lymphoma: An interim report comparing efficacy and toxicity. Haematologica 73:217-222, 1988

29. Hoofnagle J, Dusheiko G, Schafer D, et al: Reactivation of chronic hepatitis B virus infection by cancer chemotherapy. Ann Intern Med 96:447-449, 1982

30. Lok A, Liang R, Chiu E, et al: Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Gastroenterology 100:182-188, 1991

31. Liang R, Lok A, Lai C, et al: Hepatitis B infections in patients with lymphomas. Hematol Oncol 8:261-270, 1990

32. Bonadonna G, Valagussa B: Dose-response effect of adjuvant chemotherapy in breast cancer. N Engl J Med 304:10-15, 1981

33. Uyl-de Groot C, Hagenbeek A, Verdonck L, et al: Cost-effectiveness of ABMT in comparison with CHOP chemotherapy in patients with intermediate- and high-grade malignant non-Hodgkin's lymphoma (NHL). Bone Marrow Transplant 16:463-470, 1995

34. Gribben J, Neuberg D, Barber M, et al: Detection of residual lymphoma cells by polymerase chain reaction in peripheral blood is significantly less predictive for relapse than detection in bone marrow. Blood 83:3800-3807, 1994

35. Gribben J, Freedman A, Woo S, et al: All advanced stage non-Hodgkin's lymphomas with a polymerase chain reaction amplifiable breakpoint of *bcl-2* have residual cells containing the *bcl-2* rearrangement at evaluation and after treatment. Blood 78:3275-3280, 1991

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Current therapeutic paradigm for the treatment of non-Hodgkin's lymphoma.

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Patients with indolent non-Hodgkin's lymphoma may be treated with various approaches ranging from deferred initial therapy (watch and wait) to single-agent alkylating agents, radiation therapy, or combination chemotherapy. None of these approaches have produced curative results. Clearly, innovative treatment strategies are needed. The use of interferon, monoclonal antibodies with or without radioisotopes, purine analogues, and even high-dose therapy with stem-cell rescue are under investigation. Based on the fact that fewer than 40% of advanced-stage, aggressive non-Hodgkin's lymphoma patients are cured with cyclophosphamide/doxorubicin/vincristine/prednisone chemotherapy, the best approach for any patient is an experimental one. Examples include: (1) increasing the dose intensity of drugs used in standard regimens; (2) preventing the development of drug resistance; (3) combining monoclonal antibodies with chemotherapy; or (4) autologous stem-cell transplantation as a rescue from marrow-ablative chemotherapy. If a patient is not eligible or does not wish to participate in a clinical trial, cyclophosphamide/doxorubicin/vincristine/prednisone, as inadequate as it is, remains the gold standard.

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What Is New in Lymphoma?

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ABSTRACT The lymphomas are a diverse group of malignant disorders that vary with respect to their molecular features, genetics, clinical presentation, treatment approaches, and outcome. Over the past few years, there have been major advances in our understanding of the biology of these diseases, leading to a universally adopted World Health Organization classification system. New therapies are now available with the potential to improve patient outcome, and the International Prognostic Index and standardized response criteria help make clinical trials interpretable. Most notably, the chimeric antiCD20 monoclonal antibody rituximab has altered our therapeutic paradigms for B-cell disorders. Combinations of this antibody with chemotherapy and other biologic agents have shown promise in treating lymphoma. Other antibodies, radioimmunoconjugates (such as Y-90 ibritumomab tiuxetan and I-131 tositumomab), and oblimerson sodium (a *BCL-2* antisense oligonucleotide) have all shown promise. New chemotherapy regimens such as bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), agents such as gemcitabine, and monoclonal antibodies directed against CD30 are also being studied in Hodgkin Lymphoma. The challenge of clinical research is to optimize the use of these agents, select patients most likely to respond, and develop multitargeted strategies based on sound scientific rational, with the potential to increase the cure rate of patients with lymphomas. *(CA Cancer J Clin 2004;54:260–272.)* © *American Cancer Society, Inc., 2004.*

Lymphomas represent about 4% of the new cases of cancer diagnosed in the United States each year, making them the fifth most common cancer diagnosis and the fifth leading cause of cancer death. An estimated 62,250 people will be diagnosed with lymphoma in 2004, of which 54,370 are non-Hodgkin Lymphomas (NHLs), with the remainder being Hodgkin Lymphoma (HL).[1] In fact, while the incidence of most cancers is decreasing, lymphoma is one of only two tumors increasing in frequency, although the cause for this increase is unknown.

NON-HODGKIN LYMPHOMA

Classification

The NHLs represent a clinically diverse group of diseases of either B-cell or T-cell origin. For several decades, they were classified according to the International Working Formulation which was primarily based on morphologic appearance and, to a lesser extent, clinical behavior. In 1994, the Revised European-American Lymphoma (REAL) Classification distinguished lymphomas not only by histology, but by immunophenotypic, genetic, and clinical characteristics.[2] This system was further modified as the now universally accepted World Health Organization (WHO) classification (Tables 1, 2).[3]

Prognosis

In general, the NHLs are divided into diseases that are indolent, aggressive, and very aggressive. However, even within histologic subtypes, patients vary considerably with regard to outcome. In 1993, the International Prognostic Index (IPI) was published, which was developed using data from a large number of similarly treated patients with diffuse large B-cell NHL.[4] Based on age, performance status, serum lactate dehydrogenase (LDH), number of

TABLE 1 World Health Organization Classification of B-Lymphoid Neoplasms*

Precursor B-cell neoplasms
Precursor B-lymphoblastic leukemia/lymphoma
Mature (peripheral) B-cell neoplasms
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic marginal zone B-cell lymphoma
Hairy cell leukemia
Plasma cell myeloma/plasmacytoma
Extranodal marginal zone B-cell lymphoma of MALT type
Nodal marginal zone B-cell lymphoma
Follicular lymphoma
Mantle-cell lymphoma
Diffuse large B-cell lymphoma
Burkitt's lymphoma

*Common entities are shown in boldface type.

TABLE 2 World Health Organization Classification of T- and NK-Lymphoid Neoplasms*

Precursor T-cell neoplasm
Precursor T-lymphoblastic lymphoma/leukemia
Mature (peripheral) T-cell neoplasms
T-cell prolymphocytic leukemia
T-cell granular lymphocytic leukemia
Aggressive NK-cell leukemia
Adult T-cell lymphoma/leukemia
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic gamma-delta T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides/Sezary syndrome
Peripheral T-cell lymphoma, not otherwise characterized
Angioimmunoblastic T-cell lymphoma
Anaplastic large-cell lymphoma

*Common entities are shown in boldface type.

extranodal sites of involvement, and stage, patients could be separated into clinically distinct groups. More recently, a similar system has been developed for follicular lymphomas, referred to as the Follicular Lymphoma IPI (FLIPI).[5]

Newer technologies, such as DNA microarray analyses that identify genes that are either overexpressed or underexpressed by the malignant cells, have further distinguished patients into distinct risk groups even within histology.[6,7] For example, there appear to be at least two subcategories of diffuse large B-cell NHL, a germinal center B-cell type and a less favorable activated B-cell type that behave very differently, even within IPI categories.

Advances in the Treatment of Follicular NHL

The follicular lymphomas are the most common subtype of indolent NHL, representing about 30% of NHLs. They are characterized by an indolent clinical course with a median survival of 6 to 10 years. Only about 10 to 15% of patients present with limited (Stage I or nonbulky Stage II) disease. For those patients, radiation therapy may result in prolonged disease-free survival. Whether or not they are cured is controversial since relapses occur even after 10 to 20 years.

Until recently, no particular treatment clearly prolonged the survival of patients with advanced stage follicular NHL. As a result, a watch-and-wait approach was routinely recommended until treatment was clinically indicated because of disease-related symptoms, massive lymphadenopathy or hepatosplenomegaly, potential organ compromise, or peripheral blood cytopenias related to bone marrow involvement.

Despite decades of clinical research, there is still no consensus as to the optimal initial therapy for follicular and low-grade NHL. Neither an alkylating agent alone or combined with vincristine and prednisone (eg, CVP), CVP with doxorubicin (CHOP), nor fludarabine-based regimens produce a clear survival advantage over any other.

Rituximab

The availability of active monoclonal antibodies has revolutionized our approach to indolent B-cell malignancies (Table 3). Rituximab, a chimeric anti-CD20 monoclonal antibody was originally studied in patients with relapsed and refractory follicular and low-grade NHL. In the pivotal trial of 166 patients, a dose of 375 mg/m^2 weekly for four weeks was associated with responses in almost half of patients (including 6% complete remissions) with a duration of response of about 11 months.[8] This antibody has been widely adopted because of its activity and favorable toxicity profile. Most adverse reactions occur during the infusion and consist primarily of fever and chills, with occasional hypotension.

TABLE 3 Monoclonal Antibodies/RICs for non-Hodgkin Lymphoma

Antibody	Antigen	Conjugate
Rituximab	CD20	None
CAMPATH-1H	CD52	None
Epratuzumab	CD22	None, I-131, Y-90
Apolizumab (Hu1D10)	HLA-DR	None
Galiximab	CD80	None
Humanized CD20	CD20	None
Bevacizumab	VEG-F	None
Tositumomab (Bexxar)	CD20	I-131
Ibritumomab (Zevalin)	CD20	Y-90

Recent clinical trials have attempted to improve on the activity of rituximab. Increasing the number of weekly infusions from four to eight, delivery of higher doses, and increased dose density have all been unsuccessful in this regard.[9–11] Higher overall response rates have been observed with rituximab as initial therapy;[12,13] however, the duration of response has been disappointing.

The possible benefit of maintenance therapy has also been evaluated in an attempt at prolonging the time to disease progression. Hainsworth et al.[13] treated 62 patients with follicular and low grade NHL using four weekly doses of rituximab followed by four additional doses every six months for two years. The time to progression of 32 months was longer than expected. In a randomized trial, Ghielmini et al.[14] reported previously treated (n = 128) and previously untreated patients (n = 57) who received four weekly doses of rituximab, followed by a randomization to no further therapy or maintenance consisting of a single infusion of rituximab every two months for a total of eight months. The time to progression was significantly longer in the group that received maintenance; however, this benefit was primarily restricted to the previously untreated group.

The role of maintenance is confounded by the observation that 40% of patients who have experienced an initial response lasting at least six months will respond a second time, with a duration of response at least as long as the initial response.[15] Therefore, an important question is whether it is preferable to deliver maintenance or to treat disease progression instead. Hainsworth et al.[16] attempted to answer this issue in a study in which patients who were treated with an initial four weeks of rituximab were then randomized to maintenance therapy, as previously published,[13] or to retreatment on recurrence. Although response rates and time to progression favored the maintenance arm, the time to which another treatment other than rituximab was required was similar (31 months versus 27 months). The Eastern Cooperative Oncology Group (ECOG) rituximab extended schedule or retreatment trial is comparing treatment until relapse with retreatment at the time of recurrence. Therefore, at the present time, the preferable approach is not clear.

In vitro studies suggest that monoclonal antibodies such as rituximab can sensitize lymphoma cells to the effects of subsequent chemotherapy.[17,18] These observations have been supported by numerous reports in which results with rituximab plus chemotherapy appear superior to what would be expected with chemotherapy alone. The first of these regimens was reported by Czuczman et al.[19] in which 38 patients, 31 of whom were previously untreated, received CHOP plus rituximab. The overall response rate was 100%, with 58% complete remissions and a median time to progression of 8.3 years.[20] Comparable response rates can be achieved with a variety of other rituximab-based chemotherapy regimens[21–29] (Table 3). For example, Czuczman et al.[21] have also reported on the combination of fludarabine plus rituximab with a response rate of 93% and 80% complete responses. However, any differences in complete or overall response rates among the various regimens may be related to patient selection or the point in time when response is assessed, as maximal responses may occur several months following therapy.

Recent randomized trials have shown superiority for rituximab-containing regimens over chemotherapy alone. The German Low Grade Lymphoma Study Group conducted a randomized study of 394 patients who were allocated to either CHOP or R-CHOP, with a secondary randomization to a variety of postremission therapies.[28] There was no advantage from rituximab in response rate (97% versus 93%), but the combination was associated with longer

event-free survival and a trend toward longer overall survival. The variety of postremission therapies makes these data difficult to interpret.

Marcus and coworkers[27] reported on 322 patients with either intermediate or poor risk follicular NHL who received CVP either alone or with rituximab (R-CVP). The overall response rate and complete response rates for the combined modality therapy were 81% and 40%, respectively, versus 57% and 10% for CVP alone. With a median follow-up of 18 months, the R-CVP patients had a significantly longer median time to treatment failure of 27 months, versus 7 months for CVP. In addition, the median time to treatment progression was not reached for R-CVP, compared with 113 months for CVP alone. Whether an eventual prolongation in survival will be achieved with any of these regimens remains to be demonstrated by longer follow up. Thus, a clinical trial remains the preferred option for the initial therapy for patients with follicular or low-grade NHL. In the future, the optimal treatment may be determined by clinical and biological characteristics of individual patients.

However, it is clear that not all patients respond to rituximab nor benefit from the addition of that antibody to chemotherapy regimens. Patients most likely to respond can be predicted by polymorphisms for FcR gamma III, which represent the binding site for the rituximab antibody,[30] and DNA microarray signatures.[31] Moreover, the benefit of rituximab appears to be limited to patients whose tumors overexpress the *BCL-2* gene.[32] Whether these observations will determine which patients will receive rituximab remains to be seen.

Other Monoclonal Antibodies

Other unconjugated antibodies being evaluated include epratuzumab, apolizumab, alemtuzmab, galiximab, and several humanized anti-CD20 antibodies; however, a major role for any of these in NHL is uncertain at present. Alemtuzumab (Campath-1H) is a humanized monoclonal antibody directed against the CD52 antigen, whose exact function remains unknown; it is expressed on the surface of all lymphocytes, monocytes, macrophages and eosinophils. Although alemtuzumab appears to be very active in chronic lymphocytic leukemia as well as T-cell lymphomas, its activity in B-cell NHL is disappointing with partial responses of 14%.[33,34]

Epratuzumab is a humanized IgG1 monoclonal antibody directed against the CD22 antigen, expressed in a variety of lymphomas. In a dose escalation study of epratuzumab in 55 patients with indolent NHL, no dose limiting toxicities were identified. The overall response rate was 24% in patients with follicular histologies.[35] However, results from a subsequent trial designed to evaluate the combination of rituximab and epratuzumab was disappointing, suggesting that a suboptimal dose and schedule of these agents was selected.[36]

Apolizumab (Hu1D10, Remitogen) is a humanized monoclonal antibody directed against a polymorphic determinant of HLA-DR, found on both normal B cells and in about half of patients with lymphoid malignancies. Although Phase I data revealed activity in patients with relapsed or refractory indolent NHL, the Phase II data were disappointing. Furthermore, toxicities including thromboses and hemolytic uremic syndrome have hindered its development.[37–39]

CD80 is an immune costimulatory molecule present on the surface of NHL cells. Galiximab is a macaque-human chimeric anti-CD80 antibody with in vivo antilymphoma properties, which is actively being studied in patients with refractory NHL. The antibody is well tolerated except for mild fatigue, nausea, and headaches, and has single agent activity of about 15%.[40] Based on preclinical data suggesting synergy, a Phase I/II study of the combination of galiximab and rituximab has recently been completed and is undergoing analysis.[41]

Radioimmunotherapy

Despite the encouraging results with rituximab, all patients eventually become resistant to this agent. A number of reasons have been proposed including inadequate serum concentrations, loss of expression of CD20, and inaccessibility of the tumor cells to the antibody. One attempt to overcome these problems is the use of radioimmunotherapy (RIT), in which a

monoclonal antibody is conjugated to a radioisotope. RIT kills not only cells to which the antibody is bound, but as a result of a cross fire effect, also kills neighboring cells that may not express the antigen or which are inaccessible to the monoclonal antibody.

Two radioimmunoconjugates are currently commercially available. Y-90 ibritumomab tiuxetan (Zevalin) is a murine rituximab conjugated to Y-90.[42] The Zevalin regimen takes about eight days to administer. On the first day, a dose of cold (nonradioactive) anti-CD20 antibody is administered to bind nontumor CD20 sites and to facilitate better biodistribution. Because Y-90 is a beta emitter, it cannot be used for imaging; thus, indium-111 labeled ibritumomab is substituted. Two to three sets of imaging studies are performed at days 0, 2 to 3, and 6 to 7 to ensure appropriate biodistribution. On day 7 to 8, another dose of cold antibody is delivered, followed by 0.4 mCi/kg of Zevalin (not to exceed 32 mCi) for patients with platelet counts of at least 150,000/mm^3. The dose is reduced to 0.3 mCi in patients with a platelet count of 100 to 149,000/mm^3. The clinical trials thus far conducted with radioimmunoconjugates have demonstrated that they are active (more active than their cold antibody) and are useful in patients who have relapsed after, or who are refractory to, rituximab. The response rate with Zevalin in rituximab failures is reported to be 74% with 15% complete remissions.[43] In a randomized trial, 143 patients with relapsed CD20 positive NHL, without previous rituximab exposure, received either rituximab or Zevalin. Response rates were higher in the Zevalin arm at 80% compared with 56% in the rituximab arm,[44] supporting the additive benefit of the radioisotope. However, there was no difference between the arms in time to disease progression. Responses can also be safely achieved in patients who have mild thrombocytopenia (100 to 149,000/mm^3) using a lower dose of Zevalin.[45]

The major complications following Zevalin therapy relate to its myelosuppression which occurs later than with chemotherapy, at around 7 to 9 weeks following treatment. As a result, exclusionary criteria for the use of Zevalin therapy include greater than 25% bone marrow involvement, a hypocellular bone marrow (<15% cellular), platelets <100,000/mm^3, neutrophils <1,500/mm^3, extensive prior radiation therapy, and prior stem cell transplantation—the latter because the safety in this setting is unknown.

Bexxar is a conjugate of the murine anti-CD20 antibody tositumomab and I-131. Since I-131 is a gamma emitter, dosimetry can be performed to provide patient-specific dosing. As with Zevalin, treatment occurs over about a week. In contrast, thyroid protection is required with Bexxar because of the radioactive iodine. In a multicenter pivotal trial,[46] 60 heavily pretreated patients with NHL received Bexxar, with response rates of 65% with 20% complete response for the group as a whole. Patients with follicular histologies fared better, with an overall response rate of 81%. Response rates and response duration were significantly higher than with their last chemotherapy. In rituximab refractory patients, the response rate has been 63% with 29% complete response. Bexxar was subsequently approved for use in patients with relapsed/refractory follicular or transformed NHL. It has also been safely administered to previously untreated patients, with a response rate of 97% and 63% complete responses.[47] The major toxicity is myelosuppression. Bexxar can be safely administered after CHOP chemotherapy, and converts some partial responses to complete responses.[48] A randomized Phase III of a CHOP followed by Bexxar regimen versus R-CHOP is ongoing within the Southwest Oncology Group (SWOG) and the Cancer and Leukemia Group B (CALGB).

One of the major concerns with RIT is the development of secondary acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS). Published data suggest that the risk is about 1.5% with Zevalin and 6.3% with Bexxar. However, the development of this secondary malignancy likely relates to the prior treatment and may not be greater than expected from chemotherapy alone.[46,49,50]

Preliminary reports with both Zevalin and Bexxar suggest that patients can tolerate additional therapies; however, the response and toxicity data are not yet available.[51,52]

RIT may also be useful in the stem cell transplant setting. Gopal and coworkers compared their results with follicular lymphoma patients

who received high dose I-131 tositumomab with those treated using various high dose chemotherapy regimens. They found better overall survival and progression free survival, with lower toxicity in the RIT-treated population.[53]

Zevalin and Bexxar appear to have comparable activity, and their relative toxicity is being tested in a large Phase III trial. Current research is directed at trying to combine or sequence radioimmunotherapy with chemotherapy and other biologicals.

Other New Agents

Antisense Oligonucleotides

Antisense oligonucleotides are chemically modified single-strand DNA molecules that have a nucleotide sequence that is complementary to the target mRNA; therefore, they are capable of inhibiting expression of the target gene. The *BCL-2* gene is a potentially important target because it is overexpressed in most follicular B-cell NHLs and chronic lymphocytic leukemias, and in about a quarter of large B-cell NHL. *BCL-2* upregulation is thought to be responsible for maintaining the viability of tumor cells, as well as inducing a form of multidrug resistance. Elevated *BCL-2* also correlates with poor response to therapy in NHL. These observations, and others, have stimulated interest in exploring an antisense strategy against *BCL-2* and other genes important to tumor survival (Table 4).

To inhibit the target mRNA, antisense oligonucleotides must first be incorporated into cells by endocytosis. The oligonucleotide then inhibits gene expression by hybridization with the mRNA, followed by cleavage of the mRNA by recruitment of RNAse-H and other endonucleases.

G3,139 (oblimersen sodium; Genasense, Genta Incorporated, Berkeley Heights, NJ) is the first antisense molecule to be widely tested in the clinic for the treatment of human tumors. G3,139 is a phosphorothioate oligonucleotide consisting of 18 modified DNA bases (ie, 18-mer) that targets the first 6 codons of *BCL-2* mRNA to form a DNA/RNA duplex.

In the first Phase I study of G3,139 in 21 patients with NHL,[54] one patient with low-grade lymphoma who had progressive disease in nodes and bone marrow after two prior regimens attained a complete response, which has been maintained for longer than three years. Subjective improvement was also noted in the majority of patients who entered the study with tumor-related symptoms.

TABLE 4 Drugs Being Studied in non-Hodgkin Lymphoma

Drug	Mechanism of Action	Phase of Clinical Testing in Lymphoma
Bortezomib	Proteasome and NFκB inhibition	Phase II
Gallium nitrate	Inhibits ribonucleotide Reductase/DNA synthesis	Phase II
Bendamustine	Alkylating/antimetabolite	Phase II
Oblimerson sodium	*Bcl-2* antisense	Phase II
SAHA and Depsipeptide	Histone deacetylase inhibition	Phase II
CCI-779	Inhibits mTOR	Phase I/II

TABLE 5 World Health Organization Classification of Hodgkin Lymphoma*

Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
- **Nodular sclerosis Hodgkin lymphoma**
- Lymphocyte-rich classical Hodgkin lymphoma
- **Mixed cellularity Hodgkin lymphoma**
- Lymphocyte depletion Hodgkin lymphoma

*Common entities are shown in boldface type.

This *BCL-2* antisense is also active in relapsed/refractory patients with mantle cell lymphoma (MCL).[55] Side effects primarily include neutropenia, thrombocytopenia, and fatigue. Although the response rate to the single agent is modest, it augments the activity of other agents, such as rituximab, fludarabine and cyclophosphamide; therefore, this drug will have its greatest impact in combination strategies. Such multiagent regimens are currently under clinical investigation.

Vaccines

Lymphomas are characterized by their own unique idiotype, the variable region of the immunoglobulin light chain, providing the pos-

sibility for a lymphoma vaccine. In a study from Stanford, 49% of follicular NHL patients treated with this protein, conjugated to an adjuvant such as keyhole limpet hemocyanin (KLH), reacted with a cellular and humoral immune response. The ability to generate such a response appears to correlate with time to tumor progression (7.9 years versus 1.3 years).[56] Three randomized studies are evaluating the clinical benefit of the antiidiotype vaccine. In two of these, patients receive chemotherapy, followed by a rest period, and subsequently a series of vaccinations with either antiidiotype vaccine plus GM-CSF and KLH, or GM-CSF and KLH alone. In the third trial, rituximab is used as initial treatment, followed by GM-CSF and KLH with or without the antiidiotype vaccine.

Advances in the Treatment of Aggressive NHL

For decades, CHOP remained the standard regimen for patients with diffuse large B-cell NHL. Using this relatively well-tolerated regimen, about 40% of patients were cured with prolonged follow up. More intensive and aggressive regimens failed to demonstrate an advantage in randomized trials. Rituximab as a single agent was shown to have a response rate of 33% leading to interest in combining this antibody with chemotherapy. In initial studies by Vose and coworkers, the complete and overall response rates to R-CHOP were higher than would be expected with CHOP alone.[57] A marked paradigm shift followed the 2002 publication by the Groupe d'Étude des Lymphomes Agressifs (GELA) group of their randomized trial in 399 patients between the ages of 60 to 80 years with diffuse large B-cell NHL (DLBCL),[58] who received either CHOP alone or R-CHOP given on day 1 of each cycle. The complete response rate (76% versus 63%), as well as event-free and overall survival, significantly favored the combination arm. Although the difference in event-free and overall persists, there is some convergence of the overall survival curves over time. An ECOG, CALGB, and SWOG intergroup study compared CHOP with R-CHOP in 632 patients with diffuse large B-cell NHL over the age of 60 years.[59] The study design also included a secondary randomization to rituximab maintenance or observation. In contrast to the previously published GELA study, there was no difference in response rates, time to treatment failure (TTF) or survival by induction regimen. An unplanned analysis performed to remove the confounding effect of rituximab maintenance suggested a benefit for R-CHOP with respect to TTF and survival noted only in patients who did not receive rituximab during induction. Thus, these studies support R-CHOP as the new standard for patients with diffuse large B-cell NHL.

Other Drugs fro Non-Hodgkin Lymphoma in Clinical Trials

Gallium Nitrate

Gallium nitrate, the salt of the element gallium, was one of the elements tested in the National Cancer Institute (NCI) screening system found to have anticancer activity. Human clinical trials were started in 1976; the drug was found to have a profound hypocalcemic effect and was approved by the Food and Drug Administration for the treatment of hypercalcemia. Gallium has been shown to be a targeted therapy as it localizes to tumor sites, and this finding has been exploited in gallium scans. Initial Phase I and II clinical trials in a variety of malignant lymphomas used brief infusions of the drug and were associated with excessive toxicity, including optic neuritis. As a result, lower doses of the drug were delivered by continuous infusion, with responses in 43% of patients with relapsed and refractory disease.[60] A multicenter Phase II confirmatory trial using contemporary diagnostic and response criteria has just been completed in the United States and is undergoing analysis.

Bendamustine

Bendamustine is a bifunctional compound with both an alkylating nitrogen mustard group and a purinelike benzimidazole ring. It was first synthesized in 1963 in the German Democratic

Republic and has been used extensively in Germany since. Bendamustine has demonstrated activity in indolent and aggressive NHL, HL, chronic lymphocytic leukemia, and multiple myeloma.[61–64] In vitro and clinical data also support a beneficial interaction with rituximab. In a study of 63 patients with relapsed or refractory indolent NHL or mantle cell lymphoma (MCL), the response rate to this combination was 94% with 71% complete remissions.[29] This combination was extremely well tolerated. To better characterize the activity of this agent and to provide broader experience with the agent, it is now being studied alone and in combination with rituximab in Phase II trials in the United States.

Bortezomib

Bortezomib (PS-341; Velcade) is a potent, reversible inhibitor of the 26S proteasome, an enzyme important in the intracellular degradation of proteins including those involved in cell cycle regulation, transcription factor activation, apoptosis, and cell trafficking. Notable among these is NF-κB. Bortezomib is the first proteasome inhibitor to be clinically studied and has recently been approved by the Food and Drug Administration for the treatment of relapsed/refractory multiple myeloma.[65] The rationale for a study in NHL is that NF-κB is overexpressed in a number of histologies. In a report from Goy et al.[66] including 51 evaluable patients with a median of 3.5 prior treatment regimens (including eight patients with a prior autologous stem cell transplant), the response rate was 48% in those 23 evaluable patients with MCL, with 26% complete responses. A lower level of 16% was reported in small numbers of patients with other histologies. Toxicity included 22 patients with grade III thrombocytopenia, one patient with grade IV thrombocytopenia, and two patients with severe infections. A similar response rate in 10 patients with MCL has also been reported by O'Connor et al.,[67] who observed one complete and five partial responses in eight patients with follicular NHL, but failed to identify activity in three patients with small lymphocytic lymphoma. Preclinical models suggest that the activity of bortezomib is enhanced by *BCL-2* antisense, and this combination is being pursued in the clinic.

Histone Deacetylase Inhibitors

Depsipeptide (NSC 6,30176) is a bicyclic peptide originally isolated from *Chromobacterium violaceum*, strain 968, by Fujisawa Pharmaceuticals. Depsipeptide, either alone or in combination with hypomethylating agents, has been shown to induce a number of cellular proteins that may have critical effects on apoptosis, proliferation, and susceptibility to immunologic manipulation. The compound may also have antiangiogenic activity that contributes to antitumor efficacy. In a Phase I trial at the NCI, objective responses were reported in eleven patients; one complete response was reported in a peripheral T-cell lymphoma (PTCL) patient at the 12.7 mg/m^2 dose level.[68] In addition, partial responses were reported in nine cutaneous T-cell lymphoma (CTCL) patients at the 17.8 mg/m^2 dose level. Toxicities attributed to depsipeptide included anemia, leukopenia, neutropenia, thrombocytopenia, fatigue, anorexia, nausea, vomiting, elevated alanine aminotransferase/aspartate aminotransferase, increased creatine phosphokinase (CPK), hypocalcemia, asymptomatic EKG changes (ST-T wave flattening and inverted T waves), and supraventricular arrhythmias (SVT/atrial fibrillation/flutter). A Phase II trial at the NCI is ongoing.

Another histone deacetylase inhibitor, suberoylanilide hydroxamiic acid (SAHA), has demonstrated activity in NHL in Phase I trials and is now undergoing Phase II testing.[69]

Rapamycin Analog

The macrolide rapamycin (sirolimus, Rapamuner, Wyeth-Ayerst, Princeton, NJ) and its derivatives inhibit the mammalian target of rapamycin (mTOR), downregulating translation of specific mRNAs required for cell cycle progression from G1 to S phase.[70] Preclinically, mTOR inhibitors potently suppress growth and proliferation of lymphocytes and tumor cell lines.[70] Today, rapamycin is approved as an immunosuppressive drug for renal transplant

recipients. A related compound, CCI-779 (Wyeth-Ayerst, Princeton NJ) is being developed as a cancer therapeutic. In early studies, activity has been seen in mantle cell lymphoma, but with considerable myelotoxicity.[40] Studies are being designed to explore this agent at more tolerable doses.

HODGKIN LYMPHOMA

HL accounts for 14% of lymphomas with an estimated 7,880 new cases in 2004.[1] Although the etiology of HL is not known, people with a history of infectious mononucleosis have a threefold increased likelihood of developing HL, supporting a role for the Epstein-Barr virus.[71]

Classification

The WHO classification of 1999 recommended changing the name to Hodgkin Lymphoma and proposed two categories: classical HL[72] and nodular lymphocyte predominant HL. Classical HL is subdivided into nodular sclerosis (NS) HL, lymphocyte-rich classical (LRC) HL, mixed cellularity (MC) HL, and lymphocyte depletion (LD) HL. Nodular lymphocyte predominant HL is a unique form of HL that accounts for only 3 to 8% of cases of HL and generally exhibits a nodular growth pattern, with or without diffuse areas, and with rare Reed-Sternberg cells. The atypical lymphocytic and histiocytic (L&H) cells express B-cell antigens such as CD20, but rarely express CD15 or CD30, which are usually found in Classical HL. LPHL is more often localized than disseminated at diagnosis (>70% Stages I or II), exhibits a slowly progressive course, and has an extremely favorable outcome. Mediastinal masses are noted in fewer than 20% of cases. Although survival tends to be long, late relapses are more common than in other histologies, and 35% progress to a large B-cell NHL. Recent reports suggest activity for rituximab in patients with relapsed NLPHL,[73] with response rates up to 86% in one series, half of which are complete and many appear to be durable. However, while investigators from Stanford reported a high response rate of 100% with 46% complete remissions in previously treated[10] and untreated patients,[12] at a median follow-up of 13 months, 9 of the 22 patients had already relapsed.[74]

Treatment

Early Stage Disease

Radiation therapy (RT) has been the standard approach for patients with nonbulky Stage IA/IIA disease. RT achieves complete remissions in more than 95% of patients with limited disease, and the failure-free survival and overall survival rates are 75% and greater than 90%, respectively, beyond 20 years. However, radiation is associated with a number of unwanted effects, including an increased incidence of secondary malignancies. Therefore, goals of recent studies have been to determine the lowest effective dose of RT. In low risk patients, involved field irradiation has been shown to be comparable to total lymphoid irradiation. Current trials are seeking to determine whether chemotherapy can replace RT altogether. A recent randomized study compared six cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) plus involved field with four cycles and radiation, with a similar outcome. In another study, patients were treated with either four to six cycles of ABVD or standard therapy (subtotal nodal irradiation, with or without two cycles). The standard therapy produced a small but significant increase in time to progression, but with no difference in overall survival at the present time.[75]

Advanced Disease

Patients with advanced stage disease are those with Stages III or IV, the presence of B symptoms, and/or bulky disease (>10 cm at any site, >1/3 thoracic diameter). ABVD has become the standard chemotherapy because of a number of advantages; it is all-intravenous (providing better compliance), has less cumulative myelotoxicity, a lower risk of secondary malignancies (AML or solid tumors), and a lower rate of infertility compared with previous regimens (eg, mechlorethamine, vincristine,

procarbazine, and prednisone). This regimen can induce complete remissions in 80 to 85% of patients, with five-year freedom from progression of 61% and an overall five-year survival of 73%.[76]

New Treatments for Hodgkin Lymphoma

The German Hodgkin Lymphoma Group developed the intensive bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbozine, and prednisone (BEACOPP) regimen to improve on the outcome of patients with high-risk disease. Escalated BEACOPP improved failure-free survival compared with cyclophosphamide, vincristine, procarbazine, and prednisone/ABVD, but with an increased risk of secondary AML/MDS.[77] The rate of progression during treatment was only 2%, with a relapse rate of 5%, a time to treatment failure of 88% at three years and overall survival of almost 95% at five years. Current studies are looking at a regimen of four cycles of escalated BEACOPP followed by four cycles of standard BEACOPP in an attempt at reducing toxicities. Another European trial is comparing escalated BEACOPP with ABVD.

Gemcitabine

Gemcitabine is a deoxycitidine analog with single agent activity in HL. When tested in a multicenter study in 23 patients with relapsed or refractory HL, excluding patients who had undergone autologous stem-cell transplantation, the toxicity was found to be manageable, with 9% complete response and 30% partial response.[78]Pulmonary toxicity of gemcitabine is uncommon and usually mild when given as a single agent, but can be unacceptably severe when used in combinations, such as being substituted for dacarbazine in ABVD or for etoposide in BEACOPP.

Nevertheless, other combinations including gemcitabine have been tolerable with high response rates, such as the CALGB regimen of gemcitabine, navelbine, and doxil initially studied in relapsed and refractory patients. An upfront trial of doxorubicin, vinblastine, and gemcitabine in the initial treatment of low-risk patients is now active.

Anti-CD30 Monoclonal Antibodies

The CD30 antigen expressed on both Reed-Sternberg cells in HL and the malignant cells of anaplastic large cell NHL provides an excellent target for antibody therapy. Several anti-CD30 antibodies are currently being studied in clinical trials. They have been well tolerated, but the dose and schedule need to be optimized for greater activity.[79]

ASSESSMENT OF RESPONSE

Standardized guidelines for response assessment facilitate interpretation of data, comparisons of the results among various clinical trials, and identification of new agents with promising activity, and also provide a framework on which to evaluate new biologic and immunologic insights into the diseases being studied.

Some of the differences among response criteria may appear subtle but have enormous implications. For a patient to be considered as having a complete response, a protocol generally requires that all lymph nodes that were involved with NHL return to normal size. However, what is considered "normal" varies among studies. Before treatment, a normal node is 1.0 cm in diameter. Nevertheless, following treatment, nodes rarely shrink below 1.0 cm, not because they are necessarily involved with tumor, but as the result of the presence of necrosis or fibrosis. In a study using the database generated from the 166 patient rituximab pivotal trial, the complete response rate was calculated using a bidimensional normal node size of 2.0 × 2.0 cm, 1.5 × 1.5 cm, or 1.0 × 1.0 cm. Whereas the overall response rate did not change appreciably (approximately 48%), the complete response rate significantly decreased from 28% to 18% to 6%.[80]

Recently published standardized response criteria have now been incorporated into lymphoma studies and are being used by regulatory agencies to evaluate new agents.[81] Nevertheless, these recommendations were based pri-

marily on anatomic findings, including physical examination and CT scans. More recent studies suggest that positron emission tomography (PET) scans may be a more accurate way to distinguish between fibrosis and residual tumor posttreatment. In addition, whether a PET scan is positive or negative after one or two cycles of therapy is a strong predictor of outcome.[82–86] As a result, the current response criteria will be modified to incorporate PET scans.

FUTURE DIRECTIONS

This is an exciting time for the management of patients with lymphomas. Therapies are moving away from the nonspecific cytotoxic agents and toward more targeted approaches, especially in the NHLs where the malignant cells can be more reliably targeted. New classification schemes based on genetics and biology, and technologies such as genomics and proteomics, provide the opportunity to develop disease-specific and even patient-specific therapies. Not only have DNA microarrays identified different prognostic subsets, but also these subsets of patients may well be treated differently. Various approaches may be used to identify antibody-sensitive patients. At the same time, there is a growing list of new biologic and targeted chemotherapy agents. The challenge is to develop rational combinations and introduce these to patients who are most likely to benefit. The future lies in combining biologic therapies in a manner that will optimize their activity (with reduced dependence on the more toxic and nonspecific cytotoxic drugs), identifying those patients most likely to respond to those therapies, monitoring disease status, and preventing recurrence. Through these new technologies and with these unique agents, we will be able to improve the cure rate of patients with lymphomas.

REFERENCES

1. Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. CA Cancer J Clin 2004;54:8–29.

2. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84:1361–1392.

3. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the clinical advisory committee meeting - Airlie House, Virginia. J Clin Oncol 1999;17:3835–3849.

4. Shipp MA, Harrington DP, Anderson JR, et al. Development of a predictive model for aggressive lymphoma: The International Non-Hodgkin's Lymphoma Prognostic Factors Project. New Engl J Med 1993;329:987–994.

5. Colombat P, Solal-Celigny P, Roy P. Validity of the Follicular Lymphoma International Prognostic Index (FLIPI) in all age groups. Blood 2002;100:770a.

6. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503–511.

7. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for large B-cell lymphoma. New Engl J Med 2002;346:1937–1947.

8. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy of relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16:2825–2833.

9. Piro LD, White CA, Grillo-Lopez AJ, et al. Extended rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. Ann Oncol 1999;10:655–661.

10. O'Brien SM, Kantarjian H, Thomas DA, et al. Rituximab dose-escalation trial in chronic lymphocytic leukemia. J Clin Oncol 2001;19:2165–2170.

11. Byrd JC, Murphy T, Howard RS, et al. Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. J Clin Oncol 2001;19:2153–2164.

12. Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patents with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. Blood. 2001;97:101–106.

13. Hainsworth JD, Lichty S, Burris HA III, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma. J Clin Oncol 2002;20:4261–4267.

14. Ghielmini M, Schmitz S-FH, Cogliatti S, et al. Prolonged treatment with rituximab significantly improves event free survival and duration of response in patients with follicular lymphoma: a randomised SAKK trial. Blood 2002;100:161a

15. Davis TA, Grillo-López AJ, White CA, et al. Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: safety and efficacy of retreatment. J Clin Oncol 2000;18:3135–3143.

16. Hainsworth JD, Litchy S, Greco FA. Scheduled rituximab maintenance therapy versus rituximab retreatment at progression in patients with indolent non-Hodgkin's lymphoma (NHL) responding to single-agent rituximab: a randomized trial of the Minnie Pearl Cancer Research Network. Blood. 2003;102:231.

17. Demidem A, Lam T, Alas S, et al. Chimeric anti-CD20 (IDEC-C2B8) monoclonal antibody sensitizes a B cell lymphoma cell line to cell killing by cytotoxic drugs. Cancer Biother Radiopharm 1997;12:177–186.

18. Johnson TA, Press OW. Synergistic cytotoxicity of iodine-131-anti-CD20 antibodies and chemotherapy for treatment of B-cell lymphomas. Int J Cancer 2000;85:104–112.

19. Czuczman MS, Grillo-López AJ, White CA, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol 1999;17:268–276.

20. Czuczman M, Grillo-López AJ, LoBuglio AF, et al. Patients with low-grade NHL treated with rituximab + CHOP experience prolonged clinical and molecular remission. Blood 2003;102:1493a.

21. Czuczman MS, Fallon A, Mohr A, et al. Phase II study of rituximab plus fludarabine in patients (pts) with low-grade follicular lymphoma (LGL): Final report. Blood 2001;98:601a.

22. Vitolo U, Boccomini C, Ladetto M, et al. High clinical and molecular response rate in elderly patients with advanced stage follicular lymphoma treated at diagnosis with a brief chemo-immunotherapy FND + rituximab. Blood 2002;100:359a.

23. Martinelli G, Laszlo D, Mancuso P, et al. Rituximab plus chlorambucil in low-grade non

Hodgkin's lymphomas (NHL): clinical results of a phase II study. Blood 2002;100:777a.

24. Sacchi S, Tucci A, Merli F, et al. Phase II study with fludarabine and cyclophosphamide plus rituximab (FC+R) in relapsed follicular lymphoma patients. Blood 2002;100:572a.

25. Gregory SA, Venugopal P, Adler S, et al. Combined fludarabine, mitoxantrone and rituximab achieves a high response rate as initial treatment for advanced low grade non-Hodgkin's lymphoma (LGNHL). Blood 2002;100:362a.

26. Zinzani PL. A multicenter randomized trial of fludarabine and mitoxantrone (FM) plus rituximab versus CHOP plus rituximab as first-line treatment in patients with follicular lymphoma. Blood. 2002;100:93a.

27. Marcus R, Imrie K, Belch A, et al. An international multi-centre, randomized, open-label phase III trial comparing rituximab added to CVP chemotherapy to CVP chemotherapy alone in untreated stage III/IV follicular non-Hodgkin's lymphoma. Blood 2003;102:87a.

28. Hiddemann W, Dreyling M, Forstpointner R, et al. Combined immuno-chemotherapy (R-CHOP) significantly improves time to treatment failure in first line therapy of follicular lymphoma - results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). Blood 2003;102:352a.

29. Rummel MJ, Kim SZ, Chow KU, et al. Bendamustine and rituximab act synergistically in vitro and are effective in the treatment of relapsed or refractory indolent and mantle cell lymphomas. Blood. 2003;102:104a.

30. Weng WK, Levy R. Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. J Clin Oncol 2003;21:3940–3947.

31. Bohen SP, Troyanskaya OG, Alter O, et al. Variation in gene expression patterns in follicular lymphoma and response to rituximab. Proc Natl Acad Sci USA 2003;100:1926–1930.

32. Mounier N, Briere J, Gisselbrecht C, et al. Rituximab plus CHOP (R-CHOP) overcomes bcl-2-associated resistance to chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL). Blood 2003;101:4279–4284.

33. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (CAMPATH-1H) in patients who have failed fludarabine: results of a large international study. Blood 2002;99:3554–3561.

34. Lundin J, Osterborg A, Brittinger G, et al. CAMPATH-1H monoclonal antibody therapy for previously treated low-grade non-Hodgkin's lymphomas: a phase II multicenter study. J Clin Oncol 1998;16:3257–3263.

35. Leonard JP, Coleman M, Ketas JC, et al. Phase I/II trial of epratuzumab (humanized anti-CD22 antibody) in indolent non-Hodgkin's lymphoma. J Clin Oncol 2003;21:3051–3059.

36. Emmanouilides C, Leonard J, Schuster SJ, et al. Multi-center, phase 2 study of combination antibody therapy with epratuzumab plus rituximab in recurring low-grade NHL. Blood 2003;102:233a.

37. Hegde U, White T, Stetler-Stevenson M, et al. Phase I study of combination rituximab (CD20) and apolizumab (Hu1D10) monoclonal antibody therapy in previously treated B-cell lymphoma and chronic lymphocytic leukemia. Blood 2002;100(Suppl 1):358a (abstract 1389).

38. Link BK, Wang H, Byrd JC, et al. Phase I trial of humanized 1D10 (Hu1D10) monoclonal antibody targeting class II molecules in patients with relapsed lymphoma. Proc Am Soc Clin Oncol 2000;19:24a.

39. Link BK, Kahl B, Czuczman M, et al. A phase II study of Remitogen™ (Hu1D10), a humanized monoclonal antibody in patients with relapsed or refractory follicular, small lymphocytic, or marginal zone/MALT B-cell lymphomas. Blood 2001;98:606a.

40. Czuczman M, Witzig TE, Vose JM, et al. Results of a phase I/II multicenter trial of galiximab (IDEC-114, anti-CD80 antibody) therapy for relapsed or refractory follicular lymphoma. Blood 2003;102:647–648a.

41. Gordon LI, Moore JO, Cheson BD, et al. Phase I results from a multicenter trial of galiximab (anti-CD80 antibody, IDEC-114) in combination with rituximab for the treatment of follicular lymphoma. Blood 2003;102:307b.

42. Cheson BD. Radioimmunotherapy of non-Hodgkin's lymphomas. Blood 2003;101:391–398.

43. Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002;20:3262–3269.

44. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;20:2453–2463.

45. Wiseman GA, Gordon LI, Multani PS, et al. Ibritumomab tiuxetan radioimmunotherapy for patients with relapsed or refractory non-Hodgkin's lymphoma and mild thrombocytopenia: a phase II multicenter trial. Blood 2002;99:4336–4342.

46. Kaminski MS, Zelenetz AD, Press OW, et al. Pivotal study of Bexxar (Iodine I131 tositumomab) for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2001;19:3918–3928.

47. Kaminski MS, Tuck M, Regan D, et al. High response rate and durable remissions in patients with previously untreated, advanced-stage, follicular lymphoma treated with tositumomab and iodine I-131 tositumomab (Bexxar). Blood 2002;100:356a.

48. Press OW, Unger JM, Braziel RM, et al. A phase 2 trial of CHOP chemotherapy followed by tositumomab/iodine I 131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: Southwest Oncology Group protocol S9911. Blood 2003;102:1606–1612.

49. Bennett JM, Kaminski MS, Knox SJ, et al. Assessment of treatment-related myelodysplastic syndromes (tMDS) and acute myeloid leukemia (tAML) in patients with low-grade non-Hodgkin's lymphoma (LG-NHL) treated with tositumomab and iodine-131 tositumomab (the Bexxar therapeutic regimen). Blood 2003;102:91a.

50. Witzig TE, White CA, Gordon LI, et al. Safety of yttrium-90 ibritumomab tiuxetan radioimmunotherapy for relapsed low-grade, follicular, or transformed non-Hodgkin's lymphoma. J Clin Oncol 2003;21:1263–1270.

51. Kaminski M, Bahm V, Estes J, Ratanatharathorn V. Tolerance of treatment subsequent to frontline Bexxar™ (tositumomab and iodine I131 tositumomab) in patients (Pts) with follicular lymphoma. Blood 2001;98:603a.

52. Ansell SM, Ristow KM, Habermann TM, et al. Subsequent chemotherapy regimens are well tolerated after radioimmunotherapy with ^{90}Yttrium ibritumomab tiuxetan for non-Hodgkin's lymphoma. J Clin Oncol 2002;20:3885–3890.

53. Gopal AK, Gooley TA, Maloney DG, et al. High-dose radioimmunotherapy versus conventional high-dose therapy and autologous stem cell transplantation for relapsed follicular non-Hodgkin lymphoma: a multivariable cohort analysis. Blood 2003;102:2351–2357.

54. Waters JS, Webb A, Cunningham D, et al. Phase I and pharmacokinetic study of bcl-2 antisense oligonucleotide therapy in patients with non-Hodgkin's lymphoma. J Clin Oncol 2000;18:1809–1811.

55. Leonard J, Hainsworth J, Bernstein S, et al. Genasense (Oblimerson sodium, G3139) is active and well-tolerated both alone and with R-CHOP in mantle cell lymphoma. Blood 2003;102:490a.

56. Hsu FJ, Caspar C, Czerwinski D, et al. Tumor-specific idiotype vaccines in the treatment of patients with B-cell lymphoma—long term results of a clinical trial. Blood 1997;89:3129–3135.

57. Vose JM, Link BK, Grossbard ML, et al. Long term follow-up of a phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated aggressive non-Hodgkin's lymphoma (NHL). Blood 2002;100:361a.

58. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. New Engl J Med 2002;346:235– 242.

59. Habermann TM, Weller EA, Morrisson VA, et al. Phase III trial of rituximab-CHOP (R-CHOP) vs. CHOP with a second randomization to maintenance rituximab (MR) or observation in patients 60 years of age or older with diffuse large B-cell lymphoma. Blood 2003;102:8a.

60. Warrell RP Jr., Coonley CJ, Straus DJ, Young CW. Treatment of patients with advanced malignant lymphoma using gallium nitrate administration as a seven-day continuous infusion. Cancer 1983;51:1982–1987.

61. Kath R, Blumenstengel K, Fricke HJ, Hoffken K. Bendamustine monotherapy in advanced and refractory chronic lymphocytic leukemia. J Cancer Res Clin Oncol 2001;127:48–54.

62. Schwanen C, Karakas T, Begmann L. Bendamustine in the treatment of low-grade non-Hodgkin's lymphomas. Onkologie 2000;23:318–324.

63. Weidmann E, Kim SZ, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2002;13:1285–1289.

64. Bremer K. High rates of long-lasting remissions after 5-day bendamustine chemotherapy cycles in pre-treated low-grade non-Hodgkin's lymphomas. J Cancer Res Clin Oncol 2002;128:603–609.

65. Richardson PG, Barlogie B, Berenson JR, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. New Engl J Med 2003;348:2609–2617.

66. Goy A, Younes A, McLaughlin P, et al. A phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. J Clin Oncol 2004;In press.

67. O'Connor OA, Wright J, Moskowitz C, et al. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. J Clin Oncol 2004;In press.

68. Piekarz RL, Robey R, Sandor V, et al. Inhibitor of histone deacetylation, depsipeptide (FR901228), in the treatment of peripheral and cutaneous T-cell lymphoma: a case report. Blood 2001;98:2865–2868.

69. O'Connor OA, Richon V, Moskowitz C, et al. Clinical experience of the histone deacetyalse inhibitor suberoylanilide hydroxamic acid (SAHA) in heavily pre-treated patients with aggressive non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD). Blood 2002;100:301b.

70. Proud CG, Denton RM. Molecular mechanisms for the control of translation by insulin. Biochem J 1997;328:329–341.

71. Hjalgrim H, Askling J, Rostgaard K, et al. Characteristics of Hodgkin's lymphoma after infectious mononucleosis. New Engl J Med 2003;349:1324–1332.

72. Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. Tumours of Haematopoietic and Lymphoid Tissues. World Health Organization Classification of Tumours: Pathology & Genetics. Lyon, France: IARC Press; 2001.

73. Rehwald U, Schulz H, Reiser M, et al. Treatment of relapsed CD20+ Hodgkin lymphoma with the monoclonal antibody rituximab is effective and well tolerated: results of a phase 2 trial of the German Hodgkin Lymphoma study group. Blood 2003;101:420–424.

74. Ekstrand BC, Lucas JB, Horwitz SM, et al. Rituximab in lymphocyte-predominant Hodgkin disease: results of a phase 2 trial. Blood. 2003;101:4285–4289.

75. Meyer R, Gospodarowicz M, Connors J, et al. A randomized phase III comparison of single-modality ABVD with a strategy that includes radiation therapy in patients with early-stage Hodgkins disease: the HD-6 trial of the National Cancer Institute of Canada Clinical Trials Group (Eastern Cooperative Oncology Group Trial JHD06). Blood 2003;102:26a.

76. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. J Clin Oncol 2003;21:607–614.

77. Diehl V, Franklin J, Hasenclever D, et al. BEACOPP, a new dose-escalated and accelerated regimen, is at least as effective as COPP/ABVD in patients with advanced-stage Hodgkin's lymphoma: interim report from a trial of the German Hodgkin's lymphoma study group. J Clin Oncol 1998;16:3810–3821.

78. Santoro A, Bredenfeld H, Devizzi L, et al. Gemcitabine in the treatment of refractory Hodgkin's disease: results of a multicenter phase II study. J Clin Oncol 2000;18:2615–2619.

79. Bartlett NL, Bernstein SH, Leonard JP, et al. Safety, antitumor activity and pharmacokinetics of six weekly doses of SGN-30 (anti-CD30 monoclonal antibody) in patients with refractory or recurrent CD30+ hematologic malignancies. Blood 2003;102:647a.

80. Grillo-Lopez AJ, Cheson BD, Horning SJ, et al. Response criteria for NHL: importance of "normal" lymph node size and correlations with response rates. Ann Oncol 2000;11:399–408.

81. Cheson BD, Horning SJ, Coiffier B, et al. Report of an International Workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 1999;17:1244–1253.

82. Spaepen K, Stroobants S, Dupont P, et al. Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: Is [^{18}F]FDG-PET a valid alternative to conventional diagnostic methods? J Clin Oncol 2001;19:414–419.

83. Spaepen K, Stroobants S, Dupont P, et al. Early restaging positron emission tomography with 18F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. Ann Oncol 2002;13:1356–1363.

84. Spaepen K, Stroobants S, Dupont P, et al. Prognostic value of pretransplantation positron emission tomography using fluorine 18-fluorodeoxyglucose in patients with aggressive lymphoma treated with high-dose chemotherapy and stem cell transplantation. Blood 2003;102:53–59.

85. Van Den Bossche B, Lambert B, De Winter F, et al. ^{18}FDG PET versus high-dose 67Ga scintigraphy for restaging and treatment follow-up of lymphoma patients. Nuc Med Comm 2002;23:1079–1083.

86. Schot B, van Imhoff G, Pruim J, et al. Predictive value of early ^{18}F-deoxyglucose positron emission tomography in chemosensitive relapsed lymphoma. Br J Haematol 2003;123:282–287.

Merck Manual

Non-Hodgkin's lymphomas are a diverse group of cancers that develop in B or T lymphocytes.

This group of cancers is actually more than 20 different diseases, which have distinct appearances under the microscope, different cell patterns, and different clinical courses. Most non-Hodgkin's lymphomas (85%) are from B cells; less than 15% develop from T cells. Non-Hodgkin's lymphoma is more common than Hodgkin's disease. In the United States, about 65,000 new cases are diagnosed every year, and the number of new cases is increasing, especially among older people and people whose immune system is not functioning normally. Those at risk include people who have had organ transplants and some people who have been infected with the human immunodeficiency virus (HIV).

Although the cause of non-Hodgkin's lymphoma is not known, evidence strongly supports a role for viruses in some of the less common types of non-Hodgkin's lymphomas. A rare type of rapidly progressive non-Hodgkin's lymphoma, which occurs in southern Japan and the Caribbean, may result from infection with human T-cell lymphotropic virus type I (HTLV-I), a retrovirus similar to HIV. The Epstein-Barr virus is the cause of many cases of Burkitt's lymphoma, another type of non-Hodgkin's lymphoma.

Unusual Non-Hodgkin's Lymphomas

Mycosis fungoides is a rare, persistent, very slow-growing non-Hodgkin's lymphoma. Most people who develop it are older than 50. It originates from mature T lymphocytes and first affects the skin. Mycosis fungoides starts so subtly and grows so slowly that it may not be noticed initially. It causes a long-lasting, itchy rash—sometimes a small area of thickened, itchy skin that later develops nodules and slowly spreads. In some people, it develops into a form of leukemia (Sézary syndrome). In other people, it progresses to the lymph nodes and internal organs. Even with a biopsy, doctors have trouble diagnosing this disease in its early stages. However, later in the course of the disease, a biopsy shows lymphoma cells in the skin.

The thickened areas of skin are treated with a form of radiation called beta rays or with sunlight and corticosteroid drugs. Nitrogen mustard applied directly to the skin can help reduce the itching and size of the affected areas. Interferon drugs can also reduce symptoms. If the disease spreads to lymph nodes and other organs, chemotherapy may be needed. Without treatment, most people can expect to live 7 to 10 years after the diagnosis is made. Treatment does not cure the disease, but it slows it down even further.

Burkitt's lymphoma is a very fast-growing non-Hodgkin's lymphoma that originates from B lymphocytes. Burkitt's lymphoma can develop at any age, but it is most common in children and young adults, particularly males. Unlike other lymphomas, Burkitt's lymphoma has a specific geographic distribution: It is most common in central Africa and rare in the United States. The Epstein-Barr virus causes it, but it does not appear to be contagious. It is more common in people who have AIDS.

Burkitt's lymphoma grows and spreads quickly, often to the bone marrow, blood, and central nervous system. When it spreads, weakness and fatigue often develop. Large numbers of lymphoma cells may accumulate in the lymph nodes and organs of the abdomen, causing swelling. Lymphoma cells may invade the small intestine, resulting in blockage or bleeding. The neck and jaw may swell, sometimes painfully. To make the diagnosis, a doctor performs a biopsy of the abnormal tissue and orders procedures to stage the disease.

Without treatment, Burkitt's lymphoma is fatal. Surgery may be needed to remove affected parts of the intestine, which otherwise may bleed, become blocked, or rupture. Intensive chemotherapy can cure 70 to 80% of people if the disease has not spread widely. If the lymphoma has spread to the bone marrow, blood, or central nervous system at the time of diagnosis, the prognosis is much worse.

Symptoms

The first symptom is often painless enlargement of lymph nodes in the neck, under the arms, or in the groin. Enlarged lymph nodes within the chest may press against airways, causing cough and difficulty in breathing. Deep lymph nodes within the abdomen may press against various organs, causing loss of appetite, constipation, abdominal pain, or progressive swelling of the legs.

Since some lymphomas can appear in the bloodstream and bone marrow, people can develop symptoms related to too few red blood cells, white blood cells, or platelets. Too few red blood cells can cause anemia; and the person may have fatigue, shortness of breath, and pale skin. Too few white blood cells can lead to infections. Too few platelets may lead to increased bruising or bleeding. Non-Hodgkin's lymphomas also commonly invade the bone marrow, digestive tract, skin, and occasionally the nervous system, causing a variety of symptoms. Some people have persistent fever without an evident cause, the so-called fever of unknown origin. This commonly reflects an advanced stage of disease.

In children, the first symptoms—anemia, rashes, and neurologic symptoms, such as weakness and abnormal sensation—are likely to be caused by infiltration of lymphoma cells into the bone marrow, blood, skin, intestine, brain, and spinal cord. Lymph nodes that become enlarged are usually deep ones, leading to accumulation of fluid around the lungs, which causes difficulty in breathing; pressure on the intestine, which causes loss of appetite or vomiting; and blocked lymph vessels, which causes fluid retention, most noticeably in the arms and legs.

Symptoms of Non-Hodgkin's Lymphoma

Symptoms	Cause
Difficulty in breathing, swelling of the face	Enlarged lymph nodes in the chest
Loss of appetite, severe constipation, abdominal pain or distention	Enlarged lymph nodes in the abdomen
Progressive swelling of the legs	Blocked lymph vessels in the groin or abdomen
Weight loss, diarrhea, malabsorption (interference with	Invasion of the small intestine

digestion and passage of nutrients into the blood)	
Fluid accumulation around the lungs (pleural effusion)	Blocked lymph vessels in the chest
Thickened, dark, itchy areas of skin	Infiltration of the skin
Weight loss, fever, night sweats	Spread of the disease throughout the body
Anemia (an insufficient number of red blood cells)	Bleeding into the digestive tract, destruction of red blood cells by an enlarged spleen or by abnormal antibodies, destruction of bone marrow because of invasion by the lymphoma, inability of the bone marrow to produce sufficient numbers of red blood cells because of drugs or radiation therapy
Susceptibility to severe bacterial infections	Invasion of the bone marrow and lymph nodes, causing decreased antibody production

Diagnosis and Classification

Doctors perform a biopsy of an enlarged lymph node to diagnose non-Hodgkin's lymphoma and to distinguish it from Hodgkin's disease and other problems that cause enlarged lymph nodes.

Although more than 20 different diseases can be called non-Hodgkin's lymphoma, doctors sometimes group them into three broad categories. Indolent lymphomas are characterized by a survival of many years even when a person does not undergo treatment. Aggressive lymphomas are characterized by survival limited to several months in someone who goes untreated. Highly aggressive lymphomas are characterized by survival of only weeks when a person does not undergo treatment. Although non-Hodgkin's lymphomas are usually diseases of middle-aged and older people, children and young adults may develop lymphomas, and these lymphomas are commonly more aggressive.

Staging

Many people with a non-Hodgkin's lymphoma have disease that has spread at the time of diagnosis. In only 10 to 30% of people, the disease is limited to one specific area. People with the disease undergo similar staging procedures as those with Hodgkin's disease (see Lymphomas: Staging). In addition, a bone marrow biopsy is almost always performed.

Treatment and Prognosis

Almost everyone benefits from treatment. For some people, complete cure is possible; for others, treatment extends life and relieves symptoms for many years. The likelihood of cure or long-term survival depends on the type of non-Hodgkin's lymphoma and the stage when treatment starts. It is somewhat of a paradox that indolent lymphomas usually respond readily to treatment by going into remission (in which the disease is under control), often followed by long-term survival, but the disease usually is not cured. In contrast, aggressive and highly aggressive non-Hodgkin's lymphomas, which usually require very intensive treatment to achieve remission, have a good chance of being cured.

Stage I and II Non-Hodgkin's Lymphomas People with indolent lymphomas who have very limited disease (stages I and II) are often treated with radiation limited to the site of the lymphoma and adjacent areas. With this approach, 20 to 30% of people may have long-term remission and are probably cured. People with aggressive or highly aggressive lymphomas at a very early stage need to be treated with

combinations of chemotherapy, often with the addition of localized radiation therapy. With this approach, 70 to 90% of people are cured.

Stage III and IV Non-Hodgkin's Lymphomas Almost all people with indolent lymphomas have stage III or IV disease. They do not always require treatment, but they are closely monitored for evidence of complications that could signal more rapid progression of the disease. There is no evidence that early treatment in people with indolent lymphomas at more advanced stages extends survival. If the disease begins to progress more rapidly, there are many treatment choices.

Treatment may include chemotherapy with a single drug or as a combination of several different drugs. No treatment is clearly superior, so the choice of treatment is influenced by the extent of disease and the symptoms a person is having. Treatment usually produces a remission, but the average length of remission ranges from 2 to 4 years. A decision about treatment after a relapse (in which lymphoma cells reappear) again depends on the extent of the disease and the symptoms. After an initial relapse, remissions tend to become shorter.

Many new treatments are now available for indolent lymphomas. These include monoclonal antibodies, which bind to lymphoma cells and kill them. These antibodies (immunoglobulins), such as rituximab SOME TRADE NAMES RITUXAN, are given intravenously. Sometimes, the monoclonal antibodies are modified so that they can carry radioactive particles or toxic chemicals directly to the cancer cells in different parts of the body. It remains uncertain whether these monoclonal antibodies can cure non-Hodgkin's lymphomas, or if they can achieve better results when combined with chemotherapy.

Another new approach to treating indolent lymphomas involves vaccinating the person with proteins taken from his own lymphoma. The person's immune system recognizes the proteins as "foreign" and then fights the lymphoma in much the same way that it fights an infection.

For people with aggressive or highly aggressive stage III or IV non-Hodgkin's lymphomas, combinations of chemotherapy drugs are given promptly. Many potentially effective combinations of chemotherapy drugs are available. Combinations of chemotherapy drugs are often given names created by using single letters from each of the drugs that are included. For example, one of the oldest and still most

commonly used combinations is known as CHOP

cyclophosphamide SOME TRADE NAMES CYTOXAN, [hydroxy]doxorubicin (SOME TRADE NAMES ADRIAMYCIN), vincristine (SOME TRADE NAMES ONCOVIN) [Oncovin], and prednisone (SOME TRADE NAMES DELTASONE AND METICORTEN).

About 50% of people with aggressive or highly aggressive non-Hodgkin's lymphomas at an advanced stage are cured with CHOP chemotherapy. Newer combinations of drugs have not produced much improvement in cure rates. However, chemotherapy, which often causes different types of blood cells to decrease in number, is sometimes better tolerated if special proteins (called growth factors) are given to stimulate growth and development of blood cells. Chemotherapy for some people with aggressive or highly aggressive lymphomas is now combined with monoclonal antibodies. For example, results from the combination of CHOP with rituximab (SOME TRADE NAMES RITUXAN) may be better than from CHOP alone, but studies are still ongoing.

Chemotherapy at usual doses is of very limited value when relapse occurs. Many people who have a relapse of an aggressive or highly aggressive lymphoma at an advanced stage receive high-dose chemotherapy combined with autologous stem cell transplantation, involving the person's own stem cells (see Transplantation: Stem Cell Transplantation). With this type of treatment, up to 40% of people may be cured. Some stem cell transplants for people with an aggressive or highly aggressive lymphoma use stem cells from a matched or unrelated donor (allogeneic transplant), but this type of transplantation has a greater risk of complications.

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Non-Hodgkin's lymphoma: review of conventional treatments.

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The non-Hodgkin's lymphomas are a diverse groups of lymphoid neoplasms that collectively rank fifth in cancer incidence and mortality. Conventional treatment for patients with newly-diagnosed non-Hodgkin's lymphoma (NHL) includes radiation or chemotherapy. In addition, those with asymptomatic low-grade disease may follow a "watch and wait" approach. Single agent oral alkylating therapy and CVP (cyclophosphamide, vincristine, and prednisone) have become a mainstay of treatment for low-grade NHL. High intensity chemotherapy consisting of the anthracycline, doxorubicin along with cyclophosphamide, vincristine and prednisone (CHOP) is offered as standard treatment for intermediate-grade NHL. Following relapse, salvage therapy rarely results in long-term survival in patients with low-grade NHL. Up to 50% of patients die within five years of first relapse. For patients with intermediate-grade NHL who relapse after or do not respond to first-line treatment, a range of combination regimens can be offered, composed of non-cross resistant drugs not typically used during first-line treatment. However, less than half of patients with intermediate-grade disease achieve prolonged disease-free survival. With today's' conventional treatments, cure is only a possibility for a minority of patients with intermediate-grade disease and a limited group of patients with indolent NHL who are diagnosed at early stages. Novel approaches to treatment are therefore needed. Monoclonal antibodies may fulfill this need, administered either as single agents or in conjunction with conventional cytotoxic approaches. The task now lies in determining how best to use this new modality, with the hope of bringing a cure to a greater number of patients.

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Monoclonal antibodies in lymphoid neoplasia: principles for optimal combined therapy.

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Rituximab and other monoclonal antibody therapies now in development have the potential to markedly impact the treatment of non-Hodgkin's lymphoma (NHL). These agents have significant single-agent activity, distinct mechanisms of action, and, in the case of rituximab and other unconjugated antibodies, favorable toxicity profiles that are nonoverlapping with the adverse effects associated with conventional chemotherapy. These properties may allow for the use of novel combination therapies with enhanced outcomes for patients. Systematic evaluation of rationally designed combinations through randomized, prospective trials is required to determine the clinical utility of these novel agents and combinations will live up to their potential.